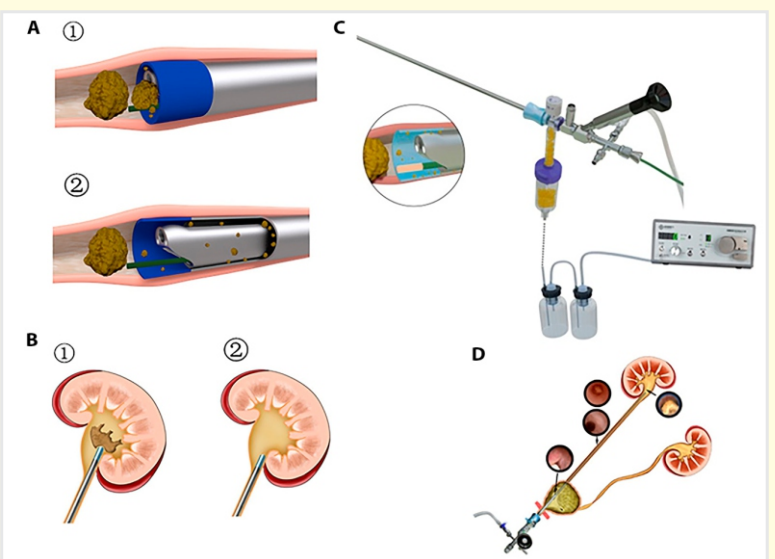
ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY
VOLUME 46, NUMBER 5, SEPTEMBER - OCTOBER, 2020



Procedures of Sotn ureterorenoscopy. A - (①, ②) Scheme of stone dust removal by the suctioning system through interspace between the shaft of the console ureterorenoscope and modified UAS. B - (①, ②) Comparison of preoperative and postoperative conditions of renal stones. C - Sotn ureterorenoscopy. D - Surgery scheme.. (*page* 789)

XXXVIII Brazilian Congress of Urology
August 28 - 31, 2021 - Brasilia - DF - Brazil

SOCIEDADE BRASILEIRA DE UROLOGIA

INTERNATIONAL

BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY - SBU

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

CONSULTING EDITORS

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL

BRAZ J UROL

Eletronic Version: Full text with fully searchable articles on-line:

https://www.intbrazjurol.com.br

Correspondence and Editorial Address:

Rua Real Grandeza, 108 - conj. 101 - 22281-034 – Rio de Janeiro – RJ – Brazil
Tel.: + 55 21 2246-4003; E-mail: brazjurol@brazjurol.com.br

The paper on which the International Braz J Urol is printed meets the requirements of ANSI/NISO Z39, 48-1992 (Permanence of Paper). Printed on acid-free paper.

The International Braz J Urol is partially supported by the Ministry of Science and Technology. National Council for Scientific and Technological Development. Editorial and Graphic Composition

The International Braz J Urol, ISSN: 1677-5538 (printed version) and ISSN: 1677-6119 (electronic version) is the Official Journal of the Brazilian Society of Urology– SBU, is published 6 times a year (bimonthly, starting in January - February).

The International Braz J Urol is indexed by: EMBASE/Excerpta Medica; SciELO, Lilacs/Latin America Index; Free Medical Journals; MD-Linx; Catálogo Latindex; SCImago, Index Medicus - NLM, PubMed/MEDLINE, PubMed/Central, ISI - Current Contents / Clinical Medicine and Science Citation Index Expanded.

ONLINE manuscript submission: **www.intbrazjurol.com.br**

DISCLAIMER

CONTENTS

Volume 46 | number 5 | September . October, 2020 | INT BRAZ J UROL

EDITORIAL IN THIS ISSUE

689 **Increase in submissions to International Brazilian Journal of Urology during Covid-19 quarentine**
Luciano A. Favorito

REVIEW ARTICLE

691 **Diagnosis accuracy of PCA3 level in patients with prostate cancer: a systematic review with meta-analysis**
Zhiqiang Qin, Jianxiang Yao, Luwei Xu, Zheng Xu, Yuzheng Ge, Liuhua Zhou, Feng Zhao, Ruipeng Jia

705 **Sarcopenia predicts prognosis of patients with renal cell carcinoma: A systematic review and meta-analysis**
Xu Hu, Du-Wu Liao, Zhi-Qiang Yang, Wei-Xiao Yang, San-Chao Xiong, Xiang Li

ORIGINAL ARTICLE

716 **The effects of menopause on the quality of life and long-term outcomes of transobturator tape treatment in women with stres urinary incontinence**
Mehmet Oguz Sahin, Volkan Sen, Bora Irer, Guner Yildiz

725 **Effects of testicular dysgenesis syndrome components on testicular germ cell tumor prognosis and oncological outcomes**
Ismail Selvi, Erdem Ozturk, Taha Numan Yikilmaz, Selcuk Sarikaya, Halil Basar

741 **Editorial Comment: Effects of testicular dysgenesis syndrome components on testicular germ cell tumor prognosis and oncological outcomes**
Andréia Cristina de Melo

743 **Self-perception, quality of life and ease of catheterization in patients with continent urinary diversion with the mitrofanoff principle**
Julián Chavarriaga, Nicolás Fernández, María A. O. Campo, John Bolivar, German Patiño, Jaime Perez

752 **Editorial Comment: Self-perception, quality of life and ease of catheterization in patients with continent urinary diversion with the mitrofanoff principle**
Antonio Carlos Moreira Amarante

754 **Comparison and trend of perioperative outcomes between robot-assisted radical prostatectomy and open radical prostatectomy: nationwide inpatient sample 2009-2014**
Yingyi Qin, Hedong Han, Yongping Xue, Cheng Wu, Xin Wei, Yuzhou Liu, Yang Cao,Yiming Ruan, Jia He

772 **Comparison of continuous eversion and inverting subepithelial suture in transverse preputial island flap urethroplasty in proximal hypospadias repair: A retrospective study**
Wenwen Han, Weiping Zhang, Ning Sun, Yanfang Yang

778 **Retrograde pyelography before radical nephroureterectomy for upper tract urothelial carcinoma is associated with intravesical tumor recurrence**
Young Hwii Ko, Phil Hyun Song, Taeyong Park, Jae Young Choi

786 Novel semirigid ureterorenoscope with irrigation and vacuum suction system: introduction and initial experience for management of upper urinary calculi
Shu Gan, Zhenlang Guo, Qianming Zou, Chiming Gu, Songtao Xiang, Siyi Li, Zhangqun Ye, Shusheng Wang

794 Editorial Comment: Novel semirigid ureterorenoscope with irrigation and vacuum suction system: introduction and initial experience for management of upper urinary calculi
Eduardo Mazzucchi

796 Development and validation a task-specific checklist for a microsurgical varicocelectomy simulation model
Marcelo Esteves Chaves Campos, Marcelo Magaldi Ribeiro de Oliveira, Augusto Barbosa Reis, Lilian Bambirra de Assis, Viacheslav Iremashvili

803 Editorial Comment: Development and validation a task-specific checklist for a microsurgical varicocelectomy simulation model
Rodrigo R. Vieiralves

805 Study of serum and urinary markers of the renin-angiotensin-aldosterone system in myelomeningocele patients with renal injury detected by DMSA
Cássia Maria Carvalho Abrantes do Amaral, Dulce Elena Casarini, Maria Cristina Andrade, Marcela Leal da Cruz, Antônio Macedo Jr.

SURGICAL TECHNIQUE

814 Transition from open partial nephrectomy directly to robotic surgery: experience of a single surgeon to achieve "TRIFECTA"
Tiago Mendonça Lopez Castilho, Gustavo Caserta Lemos, Jonathan Doyun Cha, José Roberto Colombo, Oliver Rojas Claros, Maria Beatriz Lemos, Arie Carneiro

EXPERT OPINION

822 Quick beginners guide and tips on how to write a manuscript
Leonardo Oliveira Reis

825 Primary penile Kaposi's sarcoma in HIV-seronegative patient: a case report and literature review
Gianmartin Cito, Roberto Di Costanzo, Simone Morselli, Andrea Cocci, Raffaella Santi, Gabriella Nesi, Alessandro Natali, Andrea Minervini, Marco Carini, Fabrizio Travaglini

UPDATE IN UROLOGY

Neuro-urology

843 Editorial Comment: An Effective Evidence-Based Cleaning Method for the Safe Reuse of Intermittent Urinary Catheters: In Vitro Testing
Marcio Augusto Averbeck, Blayne Welk

Endourology

845 Editorial Comment: Techniques - Ultrasound-guided percutaneous nephrolithotomy: How we do it
Alexandre Danilovic

847 Editorial Comment: The significance of intraoperative renal pelvic urine and stone cultures for patients at a high risk of post-ureteroscopy systemic inflammatory response syndrome
Alexandre Danilovic

849 Editorial Comment: Safety of a Novel Thulium Fiber Laser for Lithotripsy: An In Vitro Study on the Thermal Effect and Its Impact Factor
Alexandre Danilovic

Male Health

851 Editorial Comment: The Basic Physics of Waves, Soundwaves, and Shockwaves for Erectile Dysfunction
Valter Javaroni

Prostate Cancer

853 Editorial Comment: Cardiovascular Morbidity in a Randomized Trial Comparing GnRH Agonist and GnRH Antagonist among Patients with Advanced Prostate Cancer and Preexisting Cardiovascular Disease
Felipe Lott

855 Editorial Comment: Randomised Trial of Adjuvant Radiotherapy Following Radical Prostatectomy Versus Radical Prostatectomy Alone in Prostate Cancer Patients with Positive Margins or Extracapsular Extension
Felipe Lott

RADIOLOGY PAGE

857 Ureteroinguinal hernia with obstructive urolithiasis
JuliAnne R. Rathbun, Nanda Thimmappa, Stephen H. Weinstein, Katie S. Murray

859 Primary large cell prostate neuroendocrine carcinoma with central and nephrogenic diabetes insipidus
Cem Basatac, Sezer Sağlam, Fatma Aktepe, Haluk Akpinar

VIDEO SECTION

864 Transvaginal repair of Neobladder Vaginal Fistula with Martius Flap
Daniela Carlos, Nitya Abraham, Tian C. Zhou, Michael Hung

867 Transurethral resection of bladder tumor through artificial urinary sphincter
Kevin Heinsimer, Lucas Wiegand

868 Urolift® with median lobe resection for trilobar BPH
Julio Slongo, Aram Loeb, Rafael E Carrion

869 Combined robotic radical prostatectomy and left partial nephrectomy by a single port approach
Rair Valero, Guilherme Sawczyn, Juan Garisto, Roger Yau, Jihad Kaouk

870 Giant escrotal hidradenitis suppurativa
Iris Coello, Javier Brugarolas, Mariano Rovira, Luis Ladaria, Carlos Aliaga, Enrique Carmelo Pieras

871 How far is too far? Exploring the indications for robotic partial nephrectomy in a highly complex kidney tumor
Andrea Minervini, Antonio Andrea Grosso, Fabrizio Di Maida, Andrea Mari, Gianni Vittori, Gianluca Muto, Marco Carini

LETTER TO THE EDITOR

873 **Re: Predictive and prognostic impact of preoperative complete blood count based systemic inflammatory markers in testicular cancer**
Cengiz Beyan, Esin Beyan

875 **The old-style public health measures and the novel coronavirus outbreak**
Antonio Cassio Assis Pellizzon

877 **REPLY BY THE AUTHORS: Comment on Polygamy, Sexual Behavior in a Population Under Risk for Prostate Cancer Diagnostic: An Observational Study From the Black Sea Region in Turkey**
Abdullah Cirakoglu, Erdal Benli, Ahmet Yuce

879 **The urologist's role in the fight of COVID-19 pandemic: mandatory mindset shift on the frontline**
Alexandre Iscaife, Giovanni S. Marchini, Victor Srougi, Fabio C. M. Torricelli, Alexandre Danilovic, Fabio C. Vicentini, Marcos Machado, Marcelo Hisano, Bruno C. Tiseo, Júlio C. Bissoli, Marcello Cocuzza, Jorge Hallak, Miguel Srougi, William C. Nahas

883 **INFORMATION FOR AUTHORS**

XXXVIII CONGRESSO BRASILEIRO DE UROLOGIA

BRASÍLIA | DF

28 A 31 DE AGOSTO | 2021

CICB - CENTRO INTERNACIONAL DE CONVENÇÕES DO BRASIL

PREPARE-SE PARA 2021

SOCIEDADE BRASILEIRA DE UROLOGIA

EDITORIAL
IN THIS ISSUE

Vol. 46 (5): 689-690, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.01

Increase in submissions to International Brazilian Journal of Urology during Covid-19 quarentine

Luciano A. Favorito [1, 2]

[1] Unidade de Pesquisa Urogenital - Universidade do Estado de Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil, [2] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil

In times of Covid-19 quarentine we observed an increase in submissions around 38% to *International Brazilian Journal of Urology*, which is good news in these difficul times. The September-October number of Int Braz J Urol, the fifth under my supervision, presents original contributions with a lot of interesting papers in different fields: Prostate Cancer, Male Infertility, Female Incontinence, Renal Cell Carcinoma, Urinary Diversion, Hypospadia, Urinary Stones, Ureteral Cancer, myelomeningocele, and Testicular Cancer. The papers came from many different countries such as Brazil, USA, Turkey, China, Republic of Korea, Colombia, Spain and Canada, and as usual the editor´s comment highlights some of them.

In the present issue we present three important papers about Prostate Cancer. Dr. Qin and colleagues from China performed in page 691 (1) a nice systematic review about the prostate cancer antigen 3 (PCA3) and suggested that PCA3 was a non-invasive method with the acceptable sensitivity and specificity in the diagnosis of Prostate cancer, to distinguish between patients and healthy individuals. Dr. Yingyi Qin and collegues from China presented in page 754 (2) a nice paper about perioperative outcomes between the robot- assisted radical prostatectomy (RARP) and open radical prostatectomy (ORP) and shows that the RARP approach has lower incidence rates of perioperative complications than the ORP approach, and there is a potential decreasing tendency of complication incidence rates for the RARP. The editor in chief would like to highlight the following works too:

Dr. Chavarriaga and collegues from Colombia (3) on page 743 evaluated the self-perception of health-related quality of life (HRQoL), ease of catheterization and global and cosmetic outcomes in patient's dependent on Mitrofanoff catheterization and concluded that continent urinary diversion is associated with good HRQoL, global satisfaction, ease and painless catheterization, adequate self-perception of cosmetic outcomes and a low complication rate, remaining a safe and viable option.

Dr. Ko and Collegues (4) from Republic of Korea perfomed on page 778 a interesting study about the association between preoperative retrograde pyelography (RGP), conducted to evaluate upper tract urothelial carcinoma (UTUC), and intravesical recurrence (IVR) after radical nephroureterectomy (RNU)

and concluded that performance of RGP before RNU was shown to have a negative effect on IVR after surgery.

Dr. Gan and Collegues (5) from China performed on page 786 an interesting study about thea novel semirigid ureterorenoscope with irrigation and vacuum suction system and a modified ureteral access sheath (UAS) to overcome the deficiencies of the current procedure and to improve the efficiency and safety during treatment of upper urinary calculi. This study is on the cover in this number and concluded that this new ureterorenoscope is technically feasible, efficacious and safe for treatment of upper urinary calculi because of its advantages of high stone free rate and low complication rates.

Dr. Campos and Collegues (6) from Brazil and USA developed and validated on page 796 a new test of specific technical skills required for microsurgical varicocelectomy and suggested that the task-specific checklist of microsurgical varicocelectomy is reliable and valid in assessing microsurgical skills.

Dr. Amaral and Collegues (7) from Brazil analyzed on page 805 the serum and urinary markers of the Renin-Angiotensin-Aldosterone System (RAAS) in myelomeningocele patients with renal function abnormalities detected on DMSA and shows that the analysis of serum Angiotensin-Converting Enzyme (ACE), Angiotensin-Converting Enzyme 2 (ACE 2) and urinary ACE were not significant in patients with myelomeningocele and neurogenic bladder with renal injury previously detected by renal DMSA.

The Editor-in-chief expects everyone to enjoy reading and for sure better times will come soon.

REFERENCES

1. Qin Z, Yao J, Xu L, Xu Z, Ge Y, Zhou L, Zhao F, Jia R. Diagnosis accuracy of PCA3 level in patients with prostate cancer: a systematic review with meta-analysis. Int Braz J Urol. 2020;46:691-704.
2. Qin Y, Han H, Xue Y, Wu C, Wei X, Liu Y, Cao Y, Ruan Y1, He J. Comparison and trend of perioperative outcomes between robot-assisted radical prostatectomy and open radical prostatectomy: nationwide inpatient sample 2009-2014. Int Braz J Urol. 2020;46:754-71.
3. Chavarriaga J, Fernández N, Campo MAO, Bolivar J, Patiño G, Perez J. Self-perception, quality of life and ease of catheterization in patients with continent urinary diversion with the mitrofanoff principle. Int Braz J Urol. 2020;46:743-51.
4. Ko YH, Song PH, Park T, Choi JY. Retrograde pyelography before radical nephroureterectomy for upper tract urothelial carcinoma is associated with intravesical tumor recurrence. Int Braz J Urol. 2020;46:778-785.
5. Gan S, Guo Z, Zou Q, Gu C, Xiang S, Li S, Ye Z, Wang S. Diagnosis accuracy of PCA3 level in patients with prostate cancer: a systematic review with meta-analysis. Int Braz J Urol. 2020;46:786-93.
6. Campos MEC, de Oliveira MMR, Reis AB, de Assis LB, Iremashvili V. Development and validation a task-specific checklist for a microsurgical varicocelectomy simulation model. Int Braz J Urol. 2020;46:796-802.
7. do Amaral CMCA, Casarini DE, Andrade MC, da Cruz ML, Macedo A Jr. Study of serum and urinary markers of the renin-angiotensin-aldosterone system in myelomeningocele patients with renal injury detected by DMSA. Int Braz J Urol. 2020;46:805-13.

Luciano A. Favorito, MD, PhD

Unidade de Pesquisa Urogenital
da Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

ARTICLE INFO

Luciano A. Favorito
http://orcid.org/0000-0003-1562-6068

Int Braz J Urol. 2020; 46: 689-90

REVIEW ARTICLE

Vol. 46 (5): 691-704, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0360

Diagnosis accuracy of PCA3 level in patients with prostate cancer: a systematic review with meta-analysis

Zhiqiang Qin [1], Jianxiang Yao [2], Luwei Xu [1], Zheng Xu [1], Yuzheng Ge [1], Liuhua Zhou [1], Feng Zhao [1], Ruipeng Jia [1]

[1] Department of Urology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China; [2] Department of Urology, Huzhou first people's hospital, Huzhou, China

ABSTRACT

Background: The diagnostic value and suitability of prostate cancer antigen 3 (PCA3) for the detection of prostate cancer (PCa) have been inconsistent in previous studies. Thus, the aim of the present meta-analysis was performed to systematically evaluate the diagnostic value of PCA3 for PCa.

Materials and Methods: A meta-analysis was performed to search relevant studies using online databases EMBASE, PubMed and Web of Science published until February 1st, 2019. Ultimately, 65 studies met the inclusion criteria for this meta-analysis with 8.139 cases and 14.116 controls. The sensitivity, specificity, positive likelihood ratios (LR+), negative likelihood ratios (LR–), and other measures of PCA3 were pooled and determined to evaluate the diagnostic rate of PCa by the random-effect model.

Results: With PCA3, the pooled overall diagnostic sensitivity, specificity, LR+, LR–, and 95% confidence intervals (CIs) for predicting significant PCa were 0.68 (0.64-0.72), 0.72 (0.68-0.75), 2.41 (2.16-2.69), 0.44 (0.40-0.49), respectively. Besides, the summary diagnostic odds ratio (DOR) and 95% CIs for PCA3 was 5.44 (4.53-6.53). In addition, the area under summary receiver operating characteristic (sROC) curves and 95% CIs was 0.76 (0.72-0.79). The major design deficiencies of included studies were differential verification bias, and a lack of clear inclusion and exclusion criteria.

Conclusions: The results of this meta-analysis suggested that PCA3 was a non-invasive method with the acceptable sensitivity and specificity in the diagnosis of PCa, to distinguish between patients and healthy individuals. To validate the potential applicability of PCA3 in the diagnosis of PCa, more rigorous studies were needed to confirm these conclusions.

ARTICLE INFO

Zhiqiang Qin
http://orcid.org/0000-0001-9022-4291

Keywords:
prostate cancer antigen 3, human [Supplementary Concept]; Prostate cancer, familial [Supplementary Concept]; Meta-Analysis [Publication Type]

Int Braz J Urol. 2020; 46: 691-704

Submitted for publication:
June 05, 2019

Accepted after revision:
October 13, 2019

Published as Ahead of Print:
December 30, 2019

INTRODUCTION

Prostate cancer (PCa) is a worldwide diagnosed malignant neoplasm, which has become the second mortality rate of tumors in elderly men (1-3). The clinic symptoms of PCa are mostly similar to benign prostatic hyperplasia (BPH), which makes a difficulty for clinician to accurately distinguish PCa from BPH (4). Due to lack of effective and timely diagnostic methods, the prognosis of PCa was generally poor (4). It is quiet important for clinicians to the detection of PCa at an early stage, in order to reduce the mortality of PCa, improve the survival rate and

increase the opportunity of effective medical interventions (5-7).

Nowadays, serum prostate-specific antigen (PSA) is still widely used for PCa screening (5, 8). Serum PSA level has been widely used to detect PCa, which is an organ-specific antigen, but not a cancer-specific antigen (9). Several diseases, including BPH, prostatitis and PCa, might be associated with an elevated PSA level (5, 9). Though a high level of PSA is likely to be associated with PCa, the low specificity of PSA limits its use as a screening test and unnecessary biopsies (10). As a noninvasive diagnostic urine test, prostate cancer gene 3 (PCA3) is more accurate than PSA and can reduce the likelihood of false-positive results (11). Up to present, numerous individual studies have been performed to explore the diagnostic value of urine PCA3 in the management of PCa (12-18). However, these studies on the diagnostic performance of PCA3 have reported unclear or even conflicting results.

Based on a systematic review with meta-analysis, the objective of this study was to systematically collect the databases search results and perform an updated meta-analysis to assess the efficacy of diagnostic tests of PCA3 for the early detection of PCa.

MATERIALS AND METHODS

Literature search strategy

Studies were searched in the electronic databases EMBASE, PubMed and Web of Science up to February 1st, 2019. Available publications were identified using the following keywords or text words: 'Differential Display clone 3' or 'DD3' or 'prostate cancer antigen 3' or 'PCA3', 'prostate cancer' or 'prostate neoplasms' or 'prostate carcinoma' or 'prostatic cancer' or 'prostatic neoplasm' or 'prostatic carcinoma' or 'cancer of prostate' or 'neoplasms of prostate' or 'carcinoma of prostate', and 'sensitivity' or 'specificity' or 'false negative' or 'false positive' or 'diagnosis' or 'detection' or 'accuracy'. For assessing all relevant studies, the most eligible literatures were retrieved. Moreover, relevant articles from reference lists of selected articles were searched to identify more relevant publications and avoid relevant information missing. No language restriction was applied.

There is no registered protocol for this systematic review. This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines, which compile guidelines for the reporting of meta-analysis of observational studies. The relevant studies included in this meta-analysis are previously published, and therefore, ethical approval and informed consent are not required.

Criteria for inclusion and exclusion of published studies

The included studies must meet the inclusion criteria: (1) A case-control, nested case-control, or cohort randomized prospective or retrospective study, (2) Evaluate the diagnostic value of PCA3 in patients with PCa, (3) Available data for extraction to calculate sensitivity, specificity and other measures, (4) When duplications or the same patients used in several publications existed, the most recent or complete study was chosen in this meta-analysis. Additionally, the major exclusion criteria were as follows: (1) No available data; (2) Non-case-control studies, case reports, letters, reviewed editorial articles, (3) Duplicated publications with previous studies.

Data extraction

The extracted appropriate information and data with a standard protocol were inspected by two researchers independently, to ensure the reliability and accuracy of the results. Moreover, the controversies were reviewed and settled through discussion by a third investigator, until all problems were finally resolved. The following information from each study were extracted: name of first author, publication date, country, ethnicity, mean age, PSA value (ng/mL), assay type, sample source, sample size, cut-off value, controls value (ng/mL), PCa/non-PCa case, and raw data including true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results.

In addition, the quality of each reference was also evaluated by two investigators independently, according to the revised QUADAS tools (19). Each domain contains seven questions, whi-

ch can be answered by "yes", "no" or "not clear" that assess the quality of included studies. An answer of "yes" means a low risk of bias, whereas "no" or "not clear" means a higher risk of bias in terms of the loss of some information from each literature.

Statistical analysis

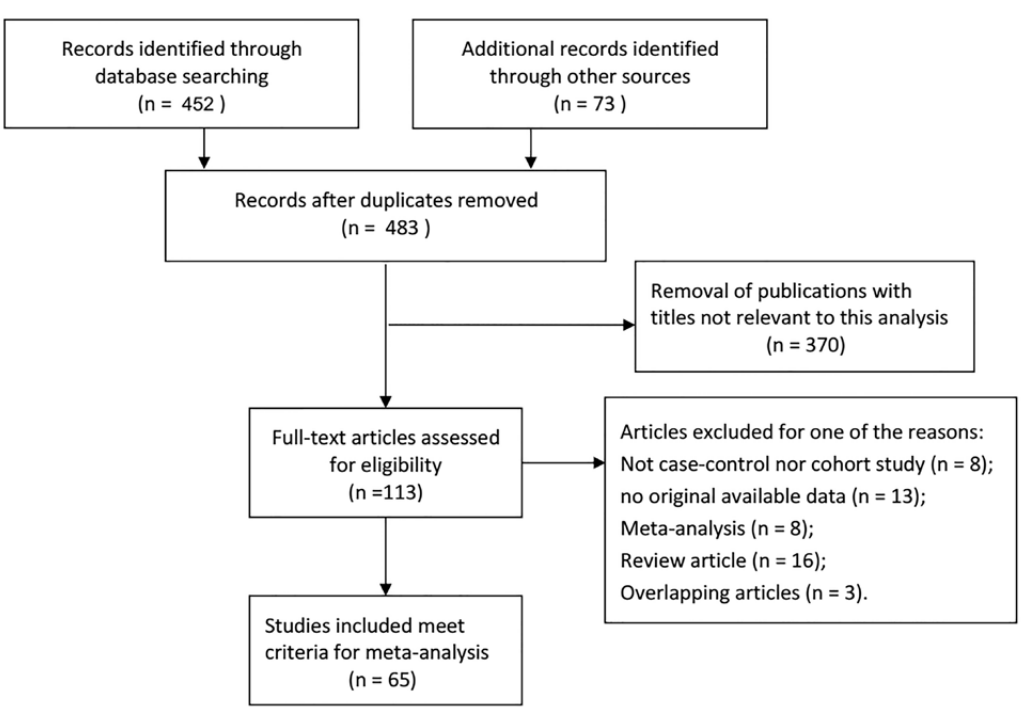
The statistical software STATA version 12.0 (StataCorp LP, College Station, TX) was performed to conduct all statistical data in this meta-analysis, and the Spearman test was used to analyze the threshold effect or the non-threshold effect. All of the statistical tests were two-sided, and P <0.05 was considered statistically significant. The pooled sensitivity, specificity, positive likelihood ratios (LR+), negative likelihood ratios (LR–), and the diagnostic odds ratio (DOR) as well as their corresponding 95% CIs were summarized to assess the diagnostic value of PCA3 in patients with PCa. Data were visualized as forest plots and receiver operating characteristic curves (ROC). The between-study heterogeneity was evaluated by Q test and I2 statistic, and P <0.05 was deemed statistically significant. As a quantitative measurement of inconsistency across different studies, I2-square value, ranged from 0 (no observed heterogeneity) to 100% (maximal heterogeneity), was also calculated. If the heterogeneity across studies was not identified, the fixed-effects model was used. Otherwise, the random-effects model was used in the meta-analysis. In addition, the summary receiver operating characteristic (sROC) curve was generated and the area under sROC curves (AUC) was calculated both overall and the subgroup analysis. Additionally, publication bias was investigated using Deek's funnel plot asymmetry test. When the P value of the Egger test was <0.05, the statistical significance was defined. Then, we replicated the funnel plot with its "missing" counterparts around the adjusted summary estimate.

RESULTS

Studies characteristics

As shown in Figure-1, 483 records were retrieved. After screening titles and abstracts of

Figure 1 - Flowchart of literature search and selection process.



relevant articles, 418 articles were excluded because these were not related to the inclusion criteria. Finally, 65 case-control studies published between 2003 and 2018 were included in the meta-analysis (11-18, 20-76). All of these studies were retrospective in design.

The present meta-analysis included 8.139 cases and 14.116 controls from a total of 65 case--control studies about evaluating the diagnostic value of PCA3 in patients with PCa, and the detailed data of each study are listed in Table-1. Based on the studies described above, we retrieved data from 22.255 patients with PCA3 test and 5.065 patients with diagnosed PCa. All the studies presented the sensitivity, specificity, LR+, LR– and cut-off points. In these studies, these assay types, such as enzyme-linked immunosorbent assay (ELISA) and reverse transcription-polymerase chain reaction (RT-PCR), were applied to detect the expression level of PCA3. Besides, fifty studies were performed on Caucasian population, ten studies were conducted on Asian population, one study was carried out on African population, and the remaining studies involved more than one race.

Quantitative synthesis results

In this meta-analysis, the random-effects model was selected to calculate the sensitivity, specificity, LR+, and LR– with corresponding 95% CIs, because of the obvious between-study heterogeneity among those studies ($P < 0.05$). The meta--analytic results showed that the pooled overall diagnostic sensitivity, specificity, LR+, LR– and 95% CIs about PCA3 for predicting significant PCa were 0.68 (0.64-0.72), 0.72 (0.68-0.75), 2.41 (2.16-2.69), 0.44 (0.40-0.49), respectively (Figure-2). Moreover, the summary diagnostic odds ratio (DOR) and 95% CIs for the diagnostic value of PCA3 in PCa patients was 5.44 (4.53-6.53) (Figure-3). In addition, AUC and 95% CI was 0.76 (0.72-0.79) (Figure-4).

Test of heterogeneity

The I2-square of sensitivity, specificity, LR+, LR– and DOR in this meta-analysis were as follows: 88.86%, 92.08%, 82.17%, 81.70% and 100%, which proved that the heterogeneity between eligible studies was significant. As a result, the random effects model was chosen to synthesize the relevant data mentioned above.

Publication bias

The potential publication bias of the included studies was evaluated through the Deek's funnel plot asymmetry test. The data of the slope coefficient of the regression line were symmetric, which suggested that the meta-analysis did not have a likelihood of publication bias (Figure-5).

DISCUSSION

Though PCa presents a slow progress, it has become a big threat to the health of men (4). Thus, the intervention at the early staging of PCa improves clinical prognosis. Serum PSA, DRE and transrectal ultrasound are still served as the screening of PCa in many countries and areas, which provides clinicians a low positive rate in the diagnosis of PCa (8). Among them, PSA is a serum marker widely used for screening of PCa in past years (4, 7). However, the proportion of positive biopsy is less than 50% in men with elevated serum PSA (10, 77). Therefore, the false-positive of PSA results may lead to unnecessary prostate biopsies and cause the complications of prostate biopsy (78). For these reasons, the searching for novel specific biomarkers of PCa has been attempted all the time.

In recent years, several serologic and pathologic biomarkers, with higher specificity than serum PSA, have been found to reduce unnecessary biopsy and inform the treatment (79, 80). Among them, PCA3 is one of the most valuable biomarkers in the detection of PCa (80). There are different expression of PCA3 gene in PCa tissue and other noncancerous tissue, which provides a great help for clinician to distinguish PCa from other prostatic diseases (80, 81). PCA3 gene is located on the long arm of chromosome 9 with 23kb long of nucleic acid and four exons and it cannot be translated into protein in normal cells (11, 82). In addition, it is a specific biomarker, over-expressed in more than 95% of PCa cells, so it can help to distinguish benign from cancerous prostate cells with an accuracy approaching 100% (83). Besides, PCA3 is also not affected by age, prostate volume or other prostatic diseases (81). In clinic, it is normally extracted

Table 1 - Characteristics and methodology assessment of individual studies included in the meta-analysis.

Year	First author	Country	Ethnicity	T Mean age (years)	T Mean PSA (ng/mL)	Assay type	Sample source	Cut-off value	Case	Control	TP	FP	FN	TN	QUADA
2018	Li	China/Asian	Asian	NR	NR	PCR	Urine	33.9	24	53	21	9	3	42	12
2017	Sanda MG	US	Caucasian / Asian/African	62 (33-85)	4.8 *(0.3-460.4)	PCR	Urine	20	264	262	104	18	160	244	10
2017	Zhou	China/Asian	Asian	65.3±7.8	7.1±1.77	PCR	Urine	23.5	33	89	27	48	6	41	11
2017	Rubio-Briones	Spain	Caucasian	61.7±6.12	4.49±1.99	PCR	Urine	35	161	396	115	186	46	210	11
2017	Bernardeau S	France	Caucasian	66.5	5.6	PCR	Urine	24	47	78	34	34	13	44	10
2017	Cao	US	Caucasian / African	63* (59–68)	NR	PCR	Urine	35	77	195	50	55	27	140	12
2017	Wang	China/Asian	Asian	45-92	NR	PCR	Urine	40.38	169	425	112	81	57	344	12
2016	Abdellaoui Maane I	Morocco	Caucasian	52-73	6.16-15.9	PCR	Tissue	cutoff 1.035	64	41	48	7	16	34	11
2016	Tan	China/Asian	Asian	71 (60-89)	32.4 (2.5-199.7)	LAMP	Serum	NR	89	101	76	8	13	93	10
2016	Nygård Y	Norway	Caucasian	64.0 (65.1*; 62.9-65.2a)	9.1 (7.2*;8.3-9.9a)	PCR	Urine	35	70	54	45	12	25	42	10
2015	Merola R	Italy	Caucasian	NR	NR	PCR	Urine	51	195	212	185	85	10	127	11
2015	Kaufmann	Germany	Caucasian	65 ± 5.6 (52–79)	10 ± 4.4 (4.0–25.0)	PCR	Urine	35	22	27	16	10	6	17	12
2015	Rubio-Briones	Spain	Caucasian	64(58-69)	5.2(4.3-7.2)	PCR	Urine	35	318	374	190	90	128	284	11
2015	Vlaeminck-Guillem V	France	Caucasian	64 ± 7(64*,59—69)	6.2 ± 4.3(6.6*,5—9.4)	PCR	Urine	35	480	535	326	155	154	380	10
2015	Coelho FF	Brasil	Caucasian	65.8±7.35	NR	PCR	Urine	cutoff 0.2219	22	37	14	9	8	28	12
2015	Huang	China/Asian	Asian	70*(51-88)	13.67(7.98–29.02)b	PCR	Urine	35	112	24	90	9	22	15	11
2014	Ruffion	France	Caucasian	63(58-67)b	5.9(4.7-7.9)b	PCR	Urine	35	274	321	173	90	101	231	11
2014	Nygård Y	Norway	Caucasian	54.0 ± 6.4; 65.1*	9.1 ± 4.7; 7.2*	PCR	Urine	35	59	65	42	18	17	47	10
2014	Wei	US	Caucasian / Asian/African	62±8	8±14	PCR	Urine	35	331	528	205	122	126	406	13
2014	Porpiglia	Italy	Caucasian	65 (60-70)b	6.9 (5.2-9.8)b	PCR	Urine	32.5	52	118	34	29	18	89	10
2014	Chevli	US	Caucasian	64.8± 9.2	6.4±23.3c	PCR	Urine	35	902	2171	478	543	424	1628	12
2013	Busetto	Italy/Rome	Caucasian	66.4 ± 5.3	6.8± 1.6	PCR	Urine	35	68	95	46	48	22	47	11
2013	Rubio-Briones	Spain	Caucasian	57.5±6.2 (57*,40-74)	4.63±2.25 (4.04*,0.37-19.5)	PCR	Urine	35	105	216	82	93	23	123	10
2013	Salagierski	Poland/ Europe	Caucasian	66.2±6.8	7.5±1.9	PCR	Urine	35	24	56	18	24	6	32	11

2013	Ochiai	Japan	Asian	69*(42–89)	7.6 *(1.4–1908)	PCR	Urine	35	264	369	176	105	88	264	11
2013	Goode	US	Caucasian	66*(41–90)	4.8*(0.1–54.2)	PCR	Urine	35	95	361	48	116	47	245	11
2013	Stephan	Germany/ Europe	Caucasian	65 *(41–81)	6.05 (0.50–19.77)	PCR	Urine	28	110	136	94	90	16	46	12
2012	Perdona	Italy/Europe	Caucasian	64.91±7.37	6.13 *(4.46–7.93)[b]	PCR	Urine	32.5	47	113	24	19	23	94	10
2012	Ng CF	China/Asian	Asian	71 (56-86)	20 / 10* (2-127)	PCR	Urine	35	17	24	12	2	5	22	12
2012	Crawford	US	Caucasian	64.4±8.6	8.0±20.0	PCR	Urine	35	802	1111	389	249	413	862	12
2012	Babera	Italy/Europe	Caucasian	64*	9.5*(3.7-28)	PCR	Urine	35	110	67	36	13	74	54	10
2012	Pepe	Italy/Europe	Caucasian	64*(48-74)	8.9*(4.5-10)	PCR	Urine	35	27	47	19	27	8	20	11
2012	Pepe	Italy/Europe	Caucasian	62.5*(48-72)	8.5 * (3.7-24)	PCR	Urine	35	32	86	23	50	9	36	11
2012	Sciarra	Italy/Europe	Caucasian	63.7±7.24	6.98±2.86	PCR	Urine	35	55	113	41	30	14	83	10
2012	Wu	US	Caucasian	63.5±7.4	11.0±8.5	PCR	Urine	35	46	57	18	13	28	44	11
2011	Vlaeminck-Guillem V	France	Caucasian	63 ± 7	6.2 ± 4.3	PCR	Urine	35	126	114	76	37	50	77	11
2011	Ochiai	Japan	Asian	66*(44-87)	7.2*(3.3-720.6)	PCR	Urine	35	35	67	26	17	9	50	11
2011	De La Taille A	France/ Germany/ Europe	Caucasian	63.0± 7.6	5.9 ± 2.1	PCR	Urine	35	207	309	133	74	74	235	12
2011	Adam	South Africa	African	67(35–89)	NR	PCR	Urine	35	44	61	34	30	10	31	11
2010	Cao	China/Asian	Asian	NR	NR	PCR	Urine	AUC:0.73	86	45	82	24	4	21	10
2010	Roobol	Netherlands/ Europe	Caucasian	70.07(63.7–74.0)	2.74 (0.2–23.0)	PCR	Urine	35	122	599	83	265	39	334	11
2010	Rigau	Spain/ Europe	Caucasian	65.7 (44–85)	11.86 (1.5–189)	PCR	Urine	35	73	142	50	58	23	84	12
2010	Auprich	France/ Germany/ Europe	Caucasian	63(35–90)	7.3(1–82.7)	PCR	Urine	35	255	366	164	110	91	256	12
2010	Ouyang	US	Caucasian	NR	NR	PCR	Urine	19	43	49	31	20	12	29	10
2010	Henderson	England/The Netherlands	Caucasian	69.9	10.1(3.03-44.2)	PCR	Urine	35	6	44	5	18	1	26	11
2010	Aubin	US	Caucasian	NR	(0.30-33.9)	PCR	Urine	35	190	882	92	189	98	693	12
2010	Morote	Spain	Caucasian	64* (39–85)	6.4*(1.5–189)	PCR	Urine	NR	83	161	75	34	8	127	11
2010	Nyberg	Sweden/ Europe	Caucasian	63 *(57–70) b	7.9 *(5.1–12.8)b	PCR	Urine	35	18	44	12	24	6	20	10
2010	Shen	China/Asian	Asian	70.3(51–86)	NR	PCR	Urine	cutoff 0.107	35	64	22	6	13	58	10
2010	Schilling	Germany/ Europe	Caucasian	NR	7.7*(2.0–46.9)	ELISA	Urine	35	18	14	17	9	1	5	10

2009	Shappell	US	Caucasian	NR	NR	PCR	Urine	35	11	19	8	3	3	16	11
2009	Wang	US	Caucasian	62 ±8.3(44-86)	8.7±12.4	PCR	Urine	35	87	100	46	20	41	80	10
2009	Mearini	Italy/Europe	Caucasian	69.1(53–83)	1.08- 172.0	PCR	Urine	AUC: 0.814	70	26	42	0	28	26	10
2008	Haese	Europe	Caucasian	64.4±6.6	8.9 ± 7.6	PCR	Urine	35	128	335	60	94	68	241	11
2008	Deras	US/ Canada	Caucasian	64 (32–89)	7.8 (0.3–484)	PCR	Urine	35	206	357	111	93	95	264	12
2008	Nakanishi	US	Caucasian / African	60 (45–70)	5.7 (1.0–27.0)	PCR	Urine	25	40	102	25	19	15	83	12
2008	Laxman	US	Caucasian	NR	NR	PCR	Urine	AUC:0.66	138	96	91	23	47	73	11
2007	Marks	US/Canada	Caucasian	64 ± 7(64*45-83)	7.4 ± 4.3(6.1*2.5-31.1)	PCR	Urine	35	60	166	35	46	25	120	11
2007	Van Gils MPMQ	Netherlands/ Europe	Caucasian	64.3±7.2	7.49 ± 2.93	PCR	Urine	58	174	360	113	122	61	238	12
2007	Van Gils MPMQ	Netherlands/ Europe	Caucasian	64±7.2	8.73± 6.61	PCR	Urine	43	23	44	14	9	9	35	10
2007	Van Gils MPMQ	Netherlands/ Europe	Caucasian	NR	NR	PCR	Urine	66	23	44	15	8	8	36	10
2006	Groskopf	US	Caucasian	67±11 (45-93)	7.7±14.1(0.4-101.7)	PCR	Urine	cutoff 0.05	16	52	11	11	5	41	12
2004	Tinzl	Austria/ Europe	Caucasian	64.7 (41-89)	0.59 -1486	PCR	Urine	cutoff 0.5	79	122	65	29	14	93	13
2004	Fradet	Canada	Caucasian	64* (40-87)	0.1-144	PCR	Urine	cutoff 0.5	152	291	100	32	52	259	12
2003	Hessels	Netherlands/ Europe	Caucasian	NR	NR	PCR	Urine	cutoff 0.2	24	84	16	14	8	70	11

*: median; **a:** 95%CI; **b:** IQR (interquartile range); **c:** missing; **d:** SEM; **AUC:** area under curve; PCA3/PSA

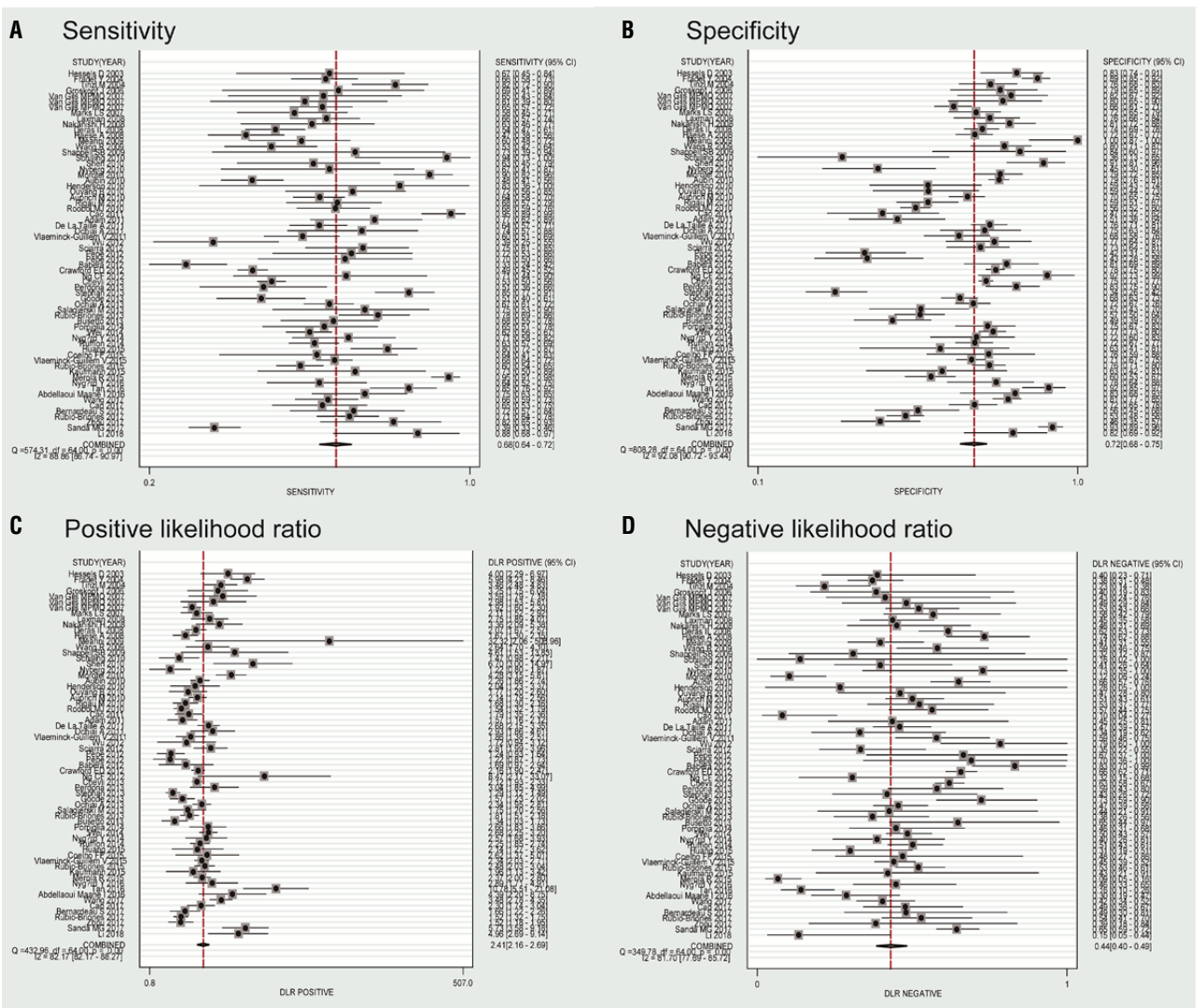
NA: data are not available; mean median (ranges); cutoff values were not provided because these studies found serum PCA3 has no correlation with PCa.

in urine samples collected after DRE (11). And PROGENSA PCA3 assay has been already widely used to measure the level of urinary PCA3, and it can also been measured in serum and tissue samples (20, 23, 84).

Over the past years, many studies have increased to evaluate the value of PCA3 in the detection of PCa. In order to elucidate the expression differences of PCA3, meta-analysis has been updated to comprehensively and systematically investigate the diagnosis accuracy of PCA3 level in PCa patients. However, the outcomes of these studies remained inconsistent and controversial. There were several variables in these studies, such as the different ethnicities, the small sample size of individual study, the possible limited effect of individual patient data, among other factors, which could have caused the limited statistical power in the published studies. Compared with previous review and meta-analysis (85-87), this meta-analysis contains more studies for the sake of the sufficient evidence of our results. Furthermore, the publication of the previous meta-analysis might generate great influence on the results. All these factors made contributions to the development of the current meta-analysis.

Compared to a single study, meta-analysis would provide more sufficient results. Thus, we suggested that there existed stronger advantages

Figure 2 - Flowchart of literature search and selection process.



to prove the relevance between the level of PCA3 and the diagnosis of PCa. Though it was deemed that PCA3 might be a valuable diagnostic biomarker of PCa in the previous studies, correlation between PCA3 level and the diagnosis of PCa remains unclear. Therefore, we need a better method for further analysis and elaboration about the diagnostic value of PCA3 for PCa. In the present meta-analysis, the summary DOR and 95% CIs for PCA3 was 5.44 (4.53-6.53), and AUC and 95% CIs was 0.76 (0.72-0.79). Thus, the above results revealed that PCA3 could be acceptable as a valuable biomarker to distinguish PCa patients from healthy individuals.

Overall, the sufficient statistical evidences including the large sample size were used to estimate the diagnostic value of PCA3 in the detection of PCa. However, several limitations were involved in this meta-analysis. First of all, the ethnicities involved in these studies were mainly Caucasians, However, Asian and African populations were included in relatively few studies. Thus, more attention should be paid to the influence of ethnicity. Secondly, there was a threshold effect and obvious heterogeneity in this meta-analysis, probably due to the large difference in reagent resource, patient characteristics, the assay type and

Figure 3 - Forest plots of summary diagnostic odds ratio of by PCA3 as a diagnostic marker for PCa in this meta-analysis. Each solid circle represents an eligible study. The size of solid circle reflects the sample size of each eligible study. Error bars represent 95% CIs.

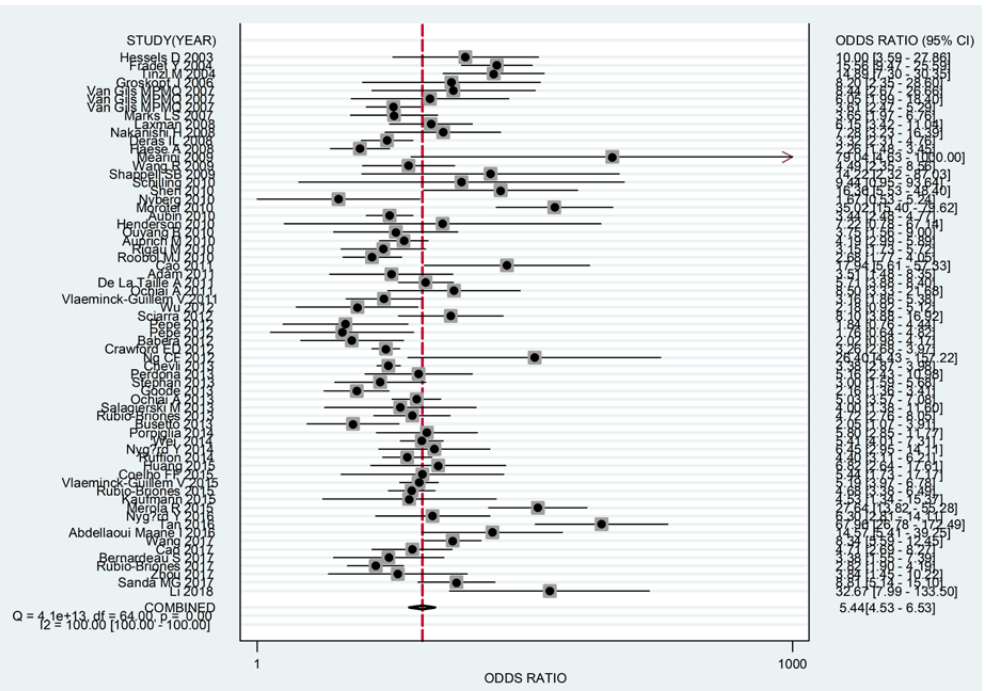


Figure 4 - Summary receiver operating characteristic curves of PCA3 for the diagnosis of PCa. Each solid circle represents an eligible study. The size of solid circle represents the sample size of each eligible study. The overall diagnostic efficiency is summarized by the regression curve.

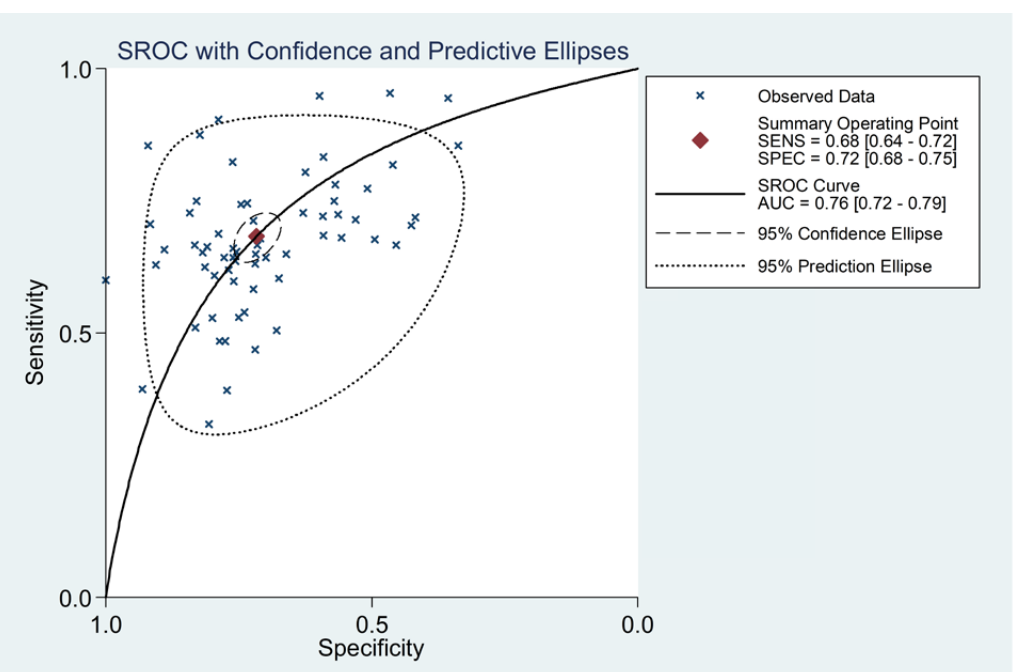
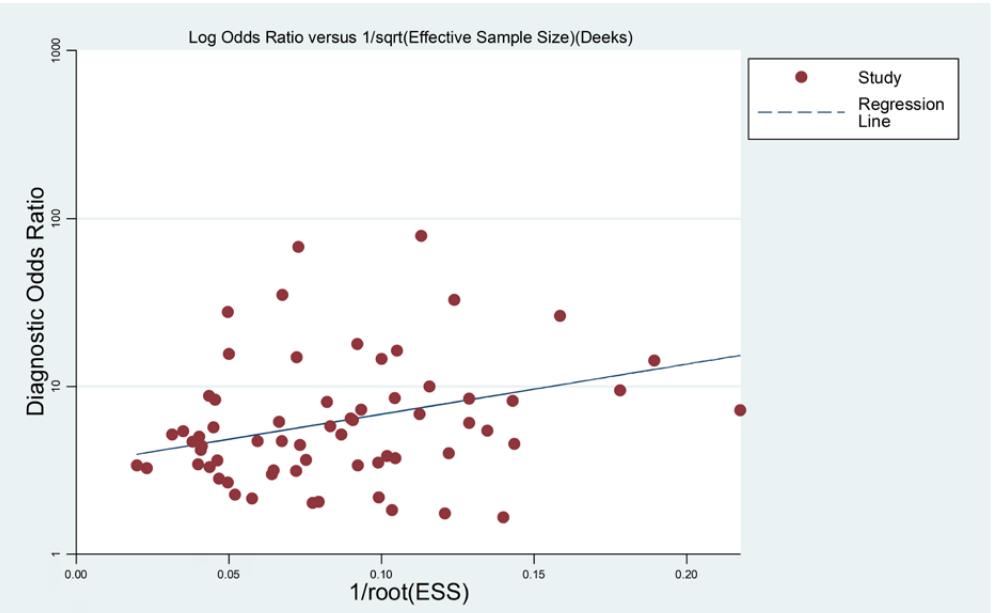


Figure 5 - Linear regression test of funnel plot asymmetry. The statistically non-significant P value of the slop coefficient indicates symmetry of the data and a low likelihood of publication bias.



the cut-off value. Moreover, the lack of sufficient data, the internal references and cut-off values were not considered in meta-regression analysis. Hence, it might reduce the reliability of our meta-analysis. In addition, more attention should be paid in further researches to the comparison of PCA3, PSA, and other biomarkers in the diagnosis of PCa. To improve reliability of the meta-analysis, well-designed studies with large sample size should be continued to evaluate the effectiveness of PCA3 in the detection of PCa in the subsequent years.

CONCLUSIONS

This meta-analysis suggested that PCA3 is acceptable as a valuable diagnostic biomarker in the management of PCa, which is a non-invasive method with the acceptable sensitivity and specificity in the diagnosis of PCa to distinguish patients from healthy individuals. To further evaluate the diagnostic value of PCA3 in patients with PCa, more well-designed studies with large sample sizes are needed to validate the effectiveness of PCA3 to differentially diagnose PCa.

ABBREVIATIONS

PCA3 = prostate cancer antigen 3;
PCa = prostate cancer;
LR+ = positive likelihood ratios;
LR– = negative likelihood ratios;
CIs = confidence intervals;
sROCs = ummary receiver operating characteristic;
AUC = area under sROC curves;
BPH = benign prostatic hyperplasia;
PSA = prostate-specific antigen;
TP = true positive;
TN = true negative;
FP = false positive;
FN = false negative;
DOR = diagnostic odds ratio;
ELISA = enzyme-linked immunosorbent assay;
RT-PCR = reverse transcription-polymerase chain reaction.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7-30.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
4. Daniyal M, Siddiqui ZA, Akram M, Asif HM, Sultana S, Khan A. Epidemiology, etiology, diagnosis and treatment of prostate cancer. Asian Pac J Cancer Prev. 2014;15:9575-8.
5. Filella X, Foj L. Prostate Cancer Detection and Prognosis: From Prostate Specific Antigen (PSA) to Exosomal Biomarkers. Int J Mol Sci. 2016;17.
6. Evangelista L, Zattoni F, Rossi E, Karnes RJ, Lowe V. Early detection of prostate cancer relapse by biochemistry and diagnostic imaging. Q J Nucl Med Mol Imaging. 2015;59:359-73.
7. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66:271-89.
8. Litwin MS, Tan HJ. The Diagnosis and Treatment of Prostate Cancer: A Review. JAMA. 2017;317:2532-2542.
9. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol. 2012;61:1079-92.
10. Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. JAMA. 2014;311:1143-9.
11. Goode RR, Marshall SJ, Duff M, Chevli E, Chevli KK. Use of PCA3 in detecting prostate cancer in initial and repeat prostate biopsy patients. Prostate. 2013;73:48-53.
12. Cao L, Lee CH, Ning J, Handy BC, Wagar EA, Meng QH. Combination of Prostate Cancer Antigen 3 and Prostate-Specific Antigen Improves Diagnostic Accuracy in Men at Risk of Prostate Cancer. Arch Pathol Lab Med. 2018;142:1106-12.
13. Li M, Zhou D, Zhang W, Gao S, Zhou X. Urine PCA3 mRNA level in diagnostic of prostate cancer. J Cancer Res Ther. 2018;14:864-6.
14. Zhou Y, Li Y, Li X, Jiang M. Urinary Biomarker Panel to Improve Accuracy in Predicting Prostate Biopsy Result in Chinese Men with PSA 4-10 ng/mL. Biomed Res Int. 2017;2017:2512536.
15. Sanda MG, Feng Z, Howard DH, Tomlins SA, Sokoll LJ, Chan DW, et al. and the EDRN-PCA3 Study Group, Bidair M, Kibel A, Lin DW, Lotan Y, Partin A, Taneja S. Association Between Combined TMPRSS2:ERG and PCA3 RNA Urinary Testing and Detection of Aggressive Prostate Cancer. JAMA Oncol. 2017;3:1085-93.
16. Rubio-Briones J, Casanova J, Martínez F, Domínguez-Escrig JL, Fernández-Serra A, Dumont R, et al. PCA3 as a second-line biomarker in a prospective controlled randomized opportunistic prostate cancer screening programme. Actas Urol Esp. 2017;41:300-8.
17. Bernardeau S, Charles T, Fromont-Hankard G, Irani J. The role of a single PCA3 test before a first negative prostate biopsy: 5-year follow-up. Prog Urol. 2017;27:325-30.
18. Wang T, Qu X, Jiang J, Gao P, Zhao D, Lian X, et al. Diagnostic significance of urinary long non-coding PCA3 RNA in prostate cancer. Oncotarget. 2017;8:58577-86.
19. Schueler S, Schuetz GM, Dewey M. The revised QUADAS-2 tool. Ann Intern Med. 2012;156:323; author reply 323-4.
20. Tan SJ, Xu LW, Xu Z, Wu JP, Liang K, Jia RP. [The value of PHI/PCA3 in the early diagnosis of prostate cancer]. Zhonghua Yi Xue Za Zhi. 2016;96:100-3.
21. Nygård Y, Haukaas SA, Halvorsen OJ, Gravdal K, Frugård J, Akslen LA, et al. A positive Real-Time Elastography (RTE) combined with a Prostate Cancer Gene 3 (PCA3) score above 35 convey a high probability of intermediate- or high-risk prostate cancer in patient admitted for primary prostate biopsy. BMC Urol. 2016;16:39.
22. Kaufmann S, Bedke J, Gatidis S, Hennenlotter J, Kramer U, Notohamiprodjo M, et al. Prostate cancer gene 3 (PCA3) is of additional predictive value in patients with PI-RADS grade III (intermediate) lesions in the MR-guided re-biopsy setting for prostate cancer. World J Urol. 2016;34:509-15.
23. Abdellaoui Maane I, El Hadi H, Qmichou Z, Al Bouzidi A, Bakri Y, Sefrioui H, et al. Evaluation of Combined Quantification of PCA3 and AMACR Gene Expression for Molecular Diagnosis of Prostate Cancer in Moroccan Patients by RT-qPCR. Asian Pac J Cancer Prev. 2016;17:5229-35.
24. Vlaeminck-Guillem V, Devonec M, Champetier D, Decaussi-Petrucci M, Paparel P, Perrin P, et al. Urinary PCA3 to predict prostate cancer in a cohort of 1015 patients. Prog Urol. 2015;25:1160-8.
25. Rubio-Briones J, Borque A, Esteban LM, Casanova J, Fernandez-Serra A, Rubio L, et al. Optimizing the clinical utility of PCA3 to diagnose prostate cancer in initial prostate biopsy. BMC Cancer. 2015;15:633.

26. Nygård Y, Haukaas SA, Eide GE, Halvorsen OJ, Gravdal K, Frugård J, et al. Prostate cancer antigen-3 (PCA3) and PCA3-based nomograms in the diagnosis of prostate cancer: an external validation of Hansen's nomogram on a Norwegian cohort. Scand J Urol. 2015;49:8-15.
27. Merola R, Tomao L, Antenucci A, Sperduti I, Sentinelli S, Masi S, et al. PCA3 in prostate cancer and tumor aggressiveness detection on 407 high-risk patients: a National Cancer Institute experience. J Exp Clin Cancer Res. 2015;34:15.
28. Huang J, Reilly KH, Zhang HZ, Wang HB. Clinical evaluation of prostate cancer gene 3 score in diagnosis among Chinese men with prostate cancer and benign prostatic hyperplasia. BMC Urol. 2015;15:118.
29. Coelho FF, Guimarães FL, Cabral WL, Salles PG, Mateo EC, Nogueira e Nogueira LM, et al. Expression of PCA3 and PSA genes as a biomarker for differential diagnosis of nodular hyperplasia and prostate cancer. Genet Mol Res. 2015;14:13519-31.
30. Wei JT, Feng Z, Partin AW, Brown E, Thompson I, Sokoll L, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol. 2014;32:4066-72.
31. Ruffion A, Perrin P, Devonec M, Champetier D, Decaussin M, Paparel P, et al. Additional value of PCA3 density to predict initial prostate biopsy outcome. World J Urol. 2014;32:917-23.
32. Rubio-Briones J, Casanova J, Dumont R, Rubio L, Fernandez-Serra A, Casanova-Salas I, et al. Optimizing prostate cancer screening; prospective randomized controlled study of the role of PSA and PCA3 testing in a sequential manner in an opportunistic screening program. Actas Urol Esp. 2014;38:217-23.
33. Porpiglia F, Russo F, Manfredi M, Mele F, Fiori C, Bollito E, et al. The roles of multiparametric magnetic resonance imaging, PCA3 and prostate health index-which is the best predictor of prostate cancer after a negative biopsy? J Urol. 2014;192:60-6.
34. Chevli KK, Duff M, Walter P, Yu C, Capuder B, Elshafei A, et al. Urinary PCA3 as a predictor of prostate cancer in a cohort of 3,073 men undergoing initial prostate biopsy. J Urol. 2014;191:1743-8.
35. Stephan C, Jung K, Semjonow A, Schulze-Forster K, Cammann H, Hu X, et al. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-specific antigen-based prostate health index for detection of prostate cancer. Clin Chem. 2013;59:280-8.
36. Salagierski M, Mulders P, Schalken JA. Predicting prostate biopsy outcome using a PCA3-based nomogram in a Polish cohort. Anticancer Res. 2013;33:553-7.
37. Perdonà S, Bruzzese D, Ferro M, Autorino R, Marino A, Mazzarella C, et al. Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Prostate. 2013;73:227-35.
38. Ochiai A, Okihara K, Kamoi K, Oikawa T, Shimazui T, Murayama S, et al. Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy. BJU Int. 2013;111:928-33.
39. Busetto GM, De Berardinis E, Sciarra A, Panebianco V, Giovannone R, Rosato S, et al. Prostate cancer gene 3 and multiparametric magnetic resonance can reduce unnecessary biopsies: decision curve analysis to evaluate predictive models. Urology. 2013;82:1355-60.
40. Wu AK, Reese AC, Cooperberg MR, Sadetsky N, Shinohara K. Utility of PCA3 in patients undergoing repeat biopsy for prostate cancer. Prostate Cancer Prostatic Dis. 2012;15:100-5.
41. Sciarra A, Panebianco V, Cattarino S, Busetto GM, De Berardinis E, Ciccariello M, et al. Multiparametric magnetic resonance imaging of the rostate can improve the predictive value of the urinary prostate cancer antigen 3 test in patients with elevated prostate-specific antigen levels and a previous negative biopsy. BJU Int. 2012;110(11):1661-5.
42. Pepe P, Fraggetta F, Galia A, Skonieczny G, Aragona F. PCA3 score and prostate cancer diagnosis at repeated saturation biopsy. Which cut-off: 20 or 35? Int Braz J Urol. 2012;38:489-95.
43. Ng CF, Yeung R, Chiu PK, Lam NY, Chow J, Chan B. The role of urine prostate cancer antigen 3 mRNA levels in the diagnosis of prostate cancer among Hong Kong Chinese patients. Hong Kong Med J. 2012;18:459-65.
44. Crawford ED, Rove KO, Trabulsi EJ, Qian J, Drewnowska KP, Kaminetsky JC, et al. Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1,962 cases. J Urol. 2012;188:1726-31.
45. Barbera M, Pepe P, Paola Q, Aragona F. PCA3 score accuracy in diagnosing prostate cancer at repeat biopsy: our experience in 177 patients. Arch Ital Urol Androl. 2012;84:227-9.
46. Vlaeminck-Guillem V, Campos-Fernandes JL, Champetier D, Chikh K, Decaussin-Petrucci M, Devonec M, et al. Value of PCA3 urinary test for prostate biopsy decision: the Lyon-Sud University Hospital experience. Ann Biol Clin (Paris). 2011;69:31-9.

47. Shen M, Chen W, Yu K, Chen Z, Zhou W, Lin X, et al. The diagnostic value of PCA3 gene-based analysis of urine sediments after digital rectal examination for prostate cancer in a Chinese population. Exp Mol Pathol. 2011;90:97-100.
48. Pepe P, Aragona F. PCA3 score vs PSA free/total accuracy in prostate cancer diagnosis at repeat saturation biopsy. Anticancer Res. 2011;31:4445-9.
49. Ochiai A, Okihara K, Kamoi K, Iwata T, Kawauchi A, Miki T, et al. Prostate cancer gene 3 urine assay for prostate cancer in Japanese men undergoing prostate biopsy. Int J Urol. 2011;18:200-5.
50. de la Taille A, Irani J, Graefen M, Chun F, de Reijke T, Kil P, et al. Clinical evaluation of the PCA3 assay in guiding initial biopsy decisions. J Urol. 2011;185:2119-25.
51. Cao DL, Ye DW, Zhang HL, Zhu Y, Wang YX, Yao XD. A multiplex model of combining gene-based, protein-based, and metabolite-based with positive and negative markers in urine for the early diagnosis of prostate cancer. Prostate. 2011;71:700-10.
52. Adam A, Engelbrecht MJ, Bornman MS, Manda SO, Moshokoa E, Feilat RA. The role of the PCA3 assay in predicting prostate biopsy outcome in a South African setting. BJU Int. 2011;108:1728-33.
53. Schilling D, Hennenlotter J, Munz M, Bökeler U, Sievert KD, Stenzl A. Interpretation of the prostate cancer gene 3 in reference to the individual clinical background: implications for daily practice. Urol Int. 2010;85:159-65.
54. Roobol MJ, Schröder FH, van Leeuwen P, Wolters T, van den Bergh RC, van Leenders GJ, et al. Performance of the prostate cancer antigen 3 (PCA3) gene and prostate-specific antigen in prescreened men: exploring the value of PCA3 for a first-line diagnostic test. Eur Urol. 2010;58:475-81.
55. Rigau M, Morote J, Mir MC, Ballesteros C, Ortega I, Sanchez A, et al. PSGR and PCA3 as biomarkers for the detection of prostate cancer in urine. Prostate. 2010;70:1760-7.
56. Nyberg M, Ulmert D, Lindgren A, Lindström U, Abrahamsson PA, Bjartell A. PCA3 as a diagnostic marker for prostate cancer: a validation study on a Swedish patient population. Scand J Urol Nephrol. 2010;44:378-83.
57. Morote J, Rigau M, Garcia M, Mir C, Ballesteros C, Planas J, et al. Behavior of the PCA3 gene in the urine of men with high grade prostatic intraepithelial neoplasia. World J Urol. 2010;28:677-80.
58. Henderson J, Ghani KR, Cook J, Fahey M, Schalken J, Thilagarajah R. The role of PCA3 testing in patients with a raised prostate-specific antigen level after Greenlight photoselective vaporization of the prostate. J Endourol. 2010;24:1821-4.
59. Auprich M, Haese A, Walz J, Pummer K, de la Taille A, Graefen M, et al. External validation of urinary PCA3-based nomograms to individually predict prostate biopsy outcome. Eur Urol. 2010;58:727-32.
60. Aubin SM, Reid J, Sarno MJ, Blase A, Aussie J, Rittenhouse H, et al. PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial. J Urol. 2010;184:1947-52.
61. Wang R, Chinnaiyan AM, Dunn RL, Wojno KJ, Wei JT. Rational approach to implementation of prostate cancer antigen 3 into clinical care. Cancer. 2009;115:3879-86.
62. Shappell SB, Fulmer J, Arguello D, Wright BS, Oppenheimer JR, Putzi MJ. PCA3 urine mRNA testing for prostate carcinoma: patterns of use by community urologists and assay performance in reference laboratory setting. Urology. 2009;73:363-8.
63. Ouyang B, Bracken B, Burke B, Chung E, Liang J, Ho SM. A duplex quantitative polymerase chain reaction assay based on quantification of alpha-methylacyl-CoA racemase transcripts and prostate cancer antigen 3 in urine sediments improved diagnostic accuracy for prostate cancer. J Urol. 2009;181:2508-13; discussion 2513-4.
64. Mearini E, Antognelli C, Del Buono C, Cochetti G, Giannantoni A, Nardelli E, et al. The combination of urine DD3(PCA3) mRNA and PSA mRNA as molecular markers of prostate cancer. Biomarkers. 2009;14:235-43.
65. van Gils MP, Hessels D, Hulsbergen-van de Kaa CA, Witjes JA, Jansen CF, Mulders PF, et al. Detailed analysis of histopathological parameters in radical prostatectomy specimens and PCA3 urine test results. Prostate. 2008;68:1215-22.
66. Nakanishi H, Groskopf J, Fritsche HA, Bhadkamkar V, Blase A, Kumar SV, et al. PCA3 molecular urine assay correlates with prostate cancer tumor volume: implication in selecting candidates for active surveillance. J Urol. 2008;179:1804-9.
67. Laxman B, Morris DS, Yu J, Siddiqui J, Cao J, Mehra R, et al. A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer. Cancer Res. 2008;68:645-9.
68. Haese A, de la Taille A, van Poppel H, Marberger M, Stenzl A, Mulders PF, et al. Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. Eur Urol. 2008;54:1081-8.
69. Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, et al. PCA3: a molecular urine assay for predicting prostate biopsy outcome. J Urol. 2008;179:1587-92.

70. van Gils MP, Hessels D, van Hooij O, Jannink SA, Peelen WP, Hanssen SL, et al. The time-resolved fluorescence-based PCA3 test on urinary sediments after digital rectal examination; a Dutch multicenter validation of the diagnostic performance. Clin Cancer Res. 2007;13:939-43.
71. van Gils MP, Cornel EB, Hessels D, Peelen WP, Witjes JA, Mulders PF, et al. Molecular PCA3 diagnostics on prostatic fluid. Prostate. 2007;67:881-7.
72. Marks LS, Fradet Y, Deras IL, Blase A, Mathis J, Aubin SM, et al. PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy. Urology. 2007;69:532-5.
73. Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S, Clark C, et al. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. Clin Chem. 2006;52:1089-95.
74. Tinzl M, Marberger M, Horvath S, Chypre C. DD3PCA3 RNA analysis in urine--a new perspective for detecting prostate cancer. Eur Urol. 2004;46:182-6; discussion 187.
75. Fradet Y, Saad F, Aprikian A, Dessureault J, Elhilali M, Trudel C, et al. uPM3, a new molecular urine test for the detection of prostate cancer. Urology. 2004;64:311-5.
76. Hessels D, Klein Gunnewiek JM, van Oort I, Karthaus HF, van Leenders GJ, van Balken B, et al. DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. Eur Urol. 2003;44:8-15; discussion 15-6.
77. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. 2010;60:70-98.
78. Pinkhasov GI, Lin YK, Palmerola R, Smith P, Mahon F, Kaag MG, et al. Complications following prostate needle biopsy requiring hospital admission or emergency department visits - experience from 1000 consecutive cases. BJU Int. 2012;110:369-74.
79. Rodriguez JF, Eggener SE. Prostate Cancer and the Evolving Role of Biomarkers in Screening and Diagnosis. Radiol Clin North Am. 2018;56:187-96.
80. Smits M, Mehra N, Sedelaar M, Gerritsen W, Schalken JA. Molecular biomarkers to guide precision medicine in localized prostate cancer. Expert Rev Mol Diagn. 2017;17:791-804.
81. Day JR, Jost M, Reynolds MA, Groskopf J, Rittenhouse H. PCA3: from basic molecular science to the clinical lab. Cancer Lett. 2011;301:1-6.
82. Hessels D, Schalken JA. The use of PCA3 in the diagnosis of prostate cancer. Nat Rev Urol. 2009;6:255-61.
83. Marks LS, Bostwick DG. Prostate Cancer Specificity of PCA3 Gene Testing: Examples from Clinical Practice. Rev Urol. 2008;10:175-81.
84. Durand X, Moutereau S, Xylinas E, de la Taille A. Progensa™ PCA3 test for prostate cancer. Expert Rev Mol Diagn. 2011;11:137-44.
85. Cui Y, Cao W, Li Q, Shen H, Liu C, Deng J, et al. Evaluation of prostate cancer antigen 3 for detecting prostate cancer: a systematic review and meta-analysis. Sci Rep. 2016;6:25776.
86. Luo Y, Gou X, Huang P, Mou C. Prostate cancer antigen 3 test for prostate biopsy decision: a systematic review and meta analysis. Chin Med J (Engl). 2014;127:1768-74.
87. Xue WJ, Ying XL, Jiang JH, Xu YH. Prostate cancer antigen 3 as a biomarker in the urine for prostate cancer diagnosis: a meta-analysis. J Cancer Res Ther. 2014;10(Suppl):C218-21.

Correspondence address:
Ruipeng Jia, MD
Department of Urology,
Nanjing First Hospital, Nanjing Medical University
Nanjing, 210006, China
E-mail: ruipengj@163.com
Tel.: + 08613851436708

REVIEW ARTICLE

Vol. 46 (5): 705-715, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0636

Sarcopenia predicts prognosis of patients with renal cell carcinoma: A systematic review and meta-analysis

Xu Hu [1], Du-Wu Liao [1], Zhi-Qiang Yang [1], Wei-Xiao Yang [1], San-Chao Xiong [1], Xiang Li [2]

[1] West China School of Medicine, West China Hospital, Sichuan University, Chengdu 610041, People's Republic of China; [2] Department of Urology, West China Hospital, West China Medical School, Sichuan University, 37 Guoxue Street, Chengdu, 610041, People's Republic of China

ABSTRACT

Sarcopenia, a concept reflecting the loss of skeletal muscle mass, was reported to be associated with the prognosis of several tumors. However, the prognostic value of sarcopenia in patients with renal cancer remains unclear. We carried out this meta-analysis and systematic review to evaluate the prognostic value of sarcopenia in patients with renal cell carcinomas. We comprehensively searched PubMed, Embase, and Cochrane Library from inception to December 2018. Hazard ratio (HR) and 95% confidence interval (CI) were pooled together. A total of 5 studies consisting of 771 patients were enrolled in this quantitative analysis, 347 (45.0%) of which had sarcopenia. Patients with sarcopenia had a worse OS compared with those without sarcopenia (HR=1.76; 95%CI, 1.35-2.31; P <0.001). In the subgroup of patients with localized and advanced/metastatic diseases, sarcopenia was also associated with poor OS (HR=1.48, P=0.039; HR=2.14, P <0.001; respectively). With a limited sample size, we did not observe difference of PFS between two groups (HR=1.56, 95% CI, 0.69-3.50, P=0.282). In the present meta-analysis, we observed that patients with sarcopenia had a worse OS compared with those without sarcopenia in RCC. Larger, preferably prospective studies, are needed to confirm and update our findings.

ARTICLE INFO

Xu Hu
http://orcid.org/0000-0003-4306-4656

Keywords:
Sarcopenia; Carcinoma, Renal Cell; Meta-Analysis [Publication Type]

Int Braz J Urol. 2020; 46: 705-15

Submitted for publication:
October 08, 2019

Accepted after revision:
November 13, 2019

Published as Ahead of Print:
March 25, 2020

INTRODUCTION

Kidney cancer is one of the leading causes of cancer-related death worldwide and mainly comprises renal cell carcinoma (RCC), with an estimated 0.4 million new cases worldwide in 2018 (1). At initial diagnosis, about 70% of patients have localized diseases and the remaining 30% have regional and metastatic diseases (2). For localized renal cancer, patients are treated with standard treatments including radical or partial nephrectomy, while approximate 20% of patients will have recurrence or progression (3-5). Treatments of advanced and metastatic RCC mainly include cytoreductive nephrectomy, targeted therapy, cytokine therapy and immunotherapy (3-4).

Reportedly, an increasing number of prognostic systems, scores and factors are associated with prognosis of patients with RCC, such as TNM stage, Fuhrman nuclear grade, the RENAL sco-

re, performance status, C-reactive protein (CRP), Glasgow prognostic score (GPS), neutrophil-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and others (3, 4, 6-9). Tsivian et al. observed that patients with a history of chemotherapy were associated with a high Fuhrman grade (10), while few studies evaluate the prognostic value of nutritious status.

Cancer cachexia and weight loss have long been regarded as adverse factors and affect the survival and therapy response of cancer patients (11, 12). Patients with advanced and metastatic RCC may have cachexia. Sarcopenia, a concept reflecting the loss of skeletal muscle mass, is a physiological change during the development of cancer cachexia (11, 13). Sarcopenia is an emerging index of nutritious status and was reported to be associated with the prognosis of several tumors including hepatocellular carcinoma, gastroesophageal tumor, colorectal cancer and urothelial carcinomas (14, 15). Based on recent studies, the prevalence of sarcopenia is relatively high in patients with RCC. In patients with localized RCC, the rate of sarcopenia was reported to be as high as 47%, and sarcopenia was observed in 29%-68% of patients with metastatic RCC (16-18). However, the prognostic value of sarcopenia in patients with renal cancer remains unclear. Some studies demonstrated sarcopenia is associated with worse survival compared with patients without sarcopenia, while others did not detect a significant association between sarcopenia and survival in patients with RCC (17-19). Therefore, in order to evaluate the prognostic value of sarcopenia in patients with RCC, we carried out this meta-analysis and systematic review by searching and pooling all available studies.

MATERIALS AND METHODS

Literatures search strategy

We conducted the study in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (20). We comprehensively searched PubMed, Embase, and Cochrane Library from inception to December 2018. We used the following items, including sarcopenia (or skeletal muscle index, muscle mass, muscle strength, muscle insufficiency, muscle depletion) and renal cancer (or tumor, carcinoma) as keywords or Mesh. Reference lists of all eligible studies were also reviewed for additional records. Two authors screened the literature independently, any discordant decisions were solved by another one.

Study selection

We included studies that met the following criteria: 1) population-based studies; 2) focused on patients with kidney cancer; 3) evaluated the prognostic value of pre-treatment sarcopenia; 4) reported available data of survival including overall survival (OS), cancer-specific survival (CSS), or progression-free survival (PFS). The exclusion criteria were as follows: 1) did not define sarcopenia; 2) did not report the outcome of survival; 3) did not provide sufficient data for analysis; 4) non-English language; 5) case report, conference abstracts, review. In cases of duplicated publications, we only enrolled the most informative and newest study.

Data extraction and quality assessment

Two reviewers extracted the following information from included studies: name of the author, enrollment data and location, study design, treatments, sample size, age, disease, and follow-up. The outcome consisted of hazard ratio (HR) and 95% confidence interval (CI) of OS, CSS and PFS. OS is defined as the time between the date of initial diagnosis of renal cancer and the date of death regardless of causes. CSS is the probability of freedom from cancer in the absence of other causes of death and only reflects the effect of renal cancer. PFS is the time during which a patient shows no signs or symptoms of the growth or the spreading of a tumor. Two authors extracted data independently, with any discrepancy resolved by consulting the third one. For random-controlled trials, we used the Cochrane Collaboration Risk of Bias Tool (21). For non-randomized studies, the Newcastle-Ottawa Quality Assessment Scale (NOS) was applied to assess study quality. Studies were evaluated on three aspects comprising selection, comparability, and exposure/outcome. We defined a score of

0-9 to each study and studies with a score of no less than 7 were regarded as good quality.

Statistical analysis

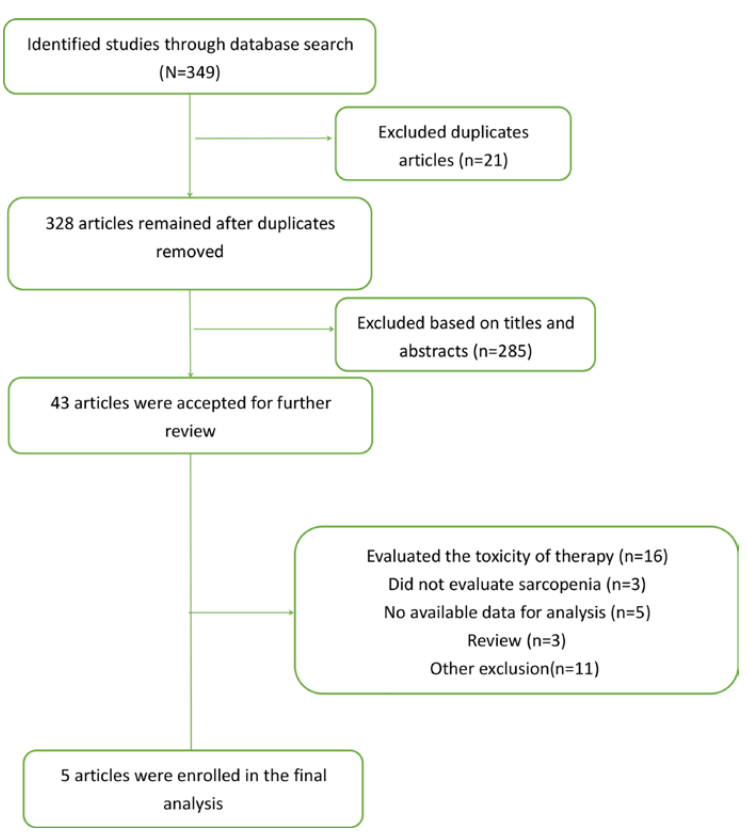
This meta-analysis was carried out by using STATA version 12® (StataCorp, College Station, TX, USA). HRs and 95%CI were applied to compare OS, CSS, and PFS between patients with or without sarcopenia. If HRs and 95%CI could not be extracted from study directly, we estimated HR and 95%CI based on the method by Tierney (22). We used Q and I^2 statistics to assess the heterogeneity among studies. If heterogeneity was observed (P <0.10 or I^2>50%), we used a random-effect model for analysis (23). Furthermore, subgroup analyses stratified by regions and stages were carried out. To further evaluate the robustness of the final results, we conducted sensitivity analysis. We used Egger's test and Begg's test to evaluate the publication bias. In cases of publication bias, the trim and fill method was applied to estimate missing studies (24). We defined a two-sided P-value <0.05 as a statistical difference. When no meta-analysis could be conducted, we only described the study results.

RESULTS

Literature search

We identified 340 literature studies through an online database search. After removing duplicated literature, 328 literature remained. Based on titles and abstracts, 285 literature were excluded and the remaining literature was further reviewed. Finally, only 5 studies comprising 771 patients were enrolled in this meta-analysis (16-19, 25). The flow chart of the literature search strategy is shown in Figure-1.

Figure 1 - Flow chart of search strategy.



Clinical characteristic of enrolled studies

A total of 771 patients were enrolled in this quantitative analysis, 347 (45.0%) of which had sarcopenia. All studies were published during the past five years. Besides, all studies were retrospective. The patients of enrolled studies were from Japan and the United States. The median ages of the included studies were similar. Only one study involved patients with localized disease (16), while the other four studies enrolled patients with advanced/metastatic diseases (17-19, 25). All studies identified sarcopenia by measuring skeletal muscle and psoas muscle at the level of the L3 using a computed tomography (CT) scan. All studies reported the outcome of OS, and two studies revealed the PFS (16, 19), while only one study demonstrated the CSS (16). Almost all studies had a relatively long follow-up duration except one (17). All studies were considered as high quality with a score of 8, 7, 8, 7, and 7. The detailed information is shown in Table-1.

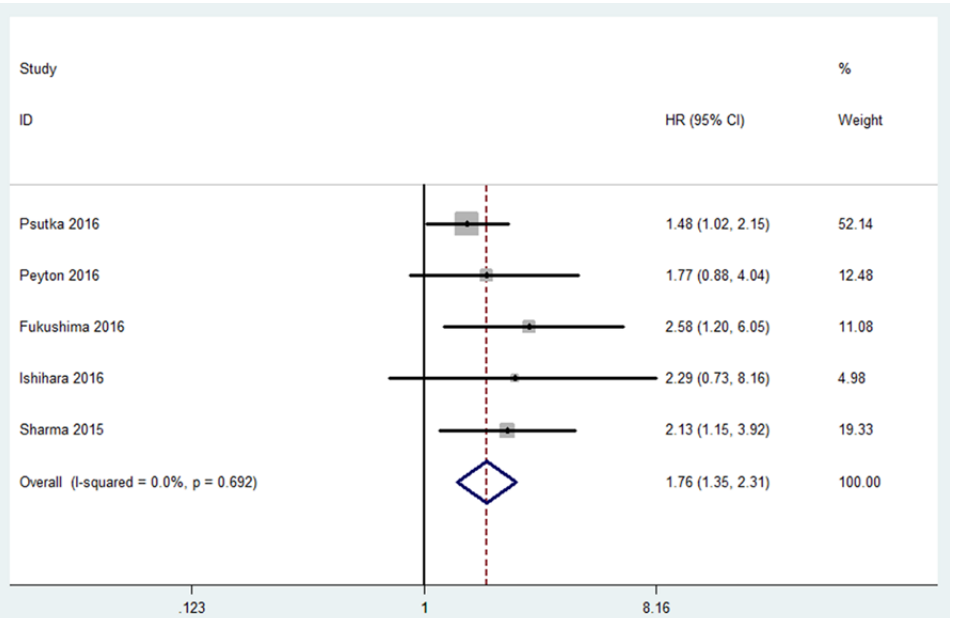
Overall survival

All studies incorporating 771 patients evaluated the difference of OS between patients with or without sarcopenia. About half of (47%) patients had sarcopenia. As indicated in Figure-2, we found that patients with sarcopenia had a worse OS compared with those without sarcopenia, the pooled HR was 1.76 (95%CI, 1.35-2.31;

Table 1 - Characteristic of included studies.

	Psutka 2016			Peyton 2016	Fukushima 2016	Ishihara 2016		Sharma 2015
Enrollment date/Location	2000 and 2010/US			2008 and 2012/ US	February 2003 and June 2014/ Japan	2007 and 2014/ Japan		March 2001and June 2014/ US
Study type	Retrospective			Retrospective	Retrospective	Retrospective		Retrospective
Treatment	Radical nephrectomy			Radical nephrectomy	cytokine therapy and targeted agents	First-Line Sunitinib		Cytoreductive nephrectomy
Number of patients	387			128	92	71		93
Age Median(IQR)	65 (55-73)			Mean (Range) 63(31-85)	Median (Range) 65(37-91)	Median (Range) 64.0 (31–79)		61(56–68)
Tumor	T1-2 N0 M0 RCC			Non T1-2 N0 M0 RCC	AnyT anyN M1 RCC	AnyT anyN M1 RCC		AnyT anyN M1 RCC
sarcopenia	180(47%)			32(25%)	63(68%)	45(63.4%)		27(29.0%)
without sarcopenia	207(53%)			96(75%)	29(32%)	26(36.6%)		66(71.0%)
Outcomes	OS	CSS	PFS	OS	OS	OS	PFS	OS
HR (95% CI)	1.48 (1.02-2.15)	1.70 (1.01-2.85)	1.10 (0.74-1.63)	1.77 (0.88–4.04)	2.58 (1.20-6.05)	2.29 (0.73-8.16)	2.54(1.19-5.65)	2.127 (1.153-3.924)
Follow-up Median IQR (months)	7.2 (5.0-9.7) years			Median(Range) 48.3 (0.1-78.7)	Median (Range) 19(1-142)	Median (Range) 17.0(2.24-65.6)		13(5-31)
NOS	8			7	8	7		7

Figure 2 - Meta-analysis of the association between sarcopenia and OS in patients with RCC.



P <0.001). There was no significant heterogeneity among studies (I^2=0%; P=0.692), as a result, we used the fixed-effect model.

Cancer-specific survival

Only one study involved the CSS, so we did not perform the meta-analysis. Psutka et al. observed that sarcopenia was associated with increased cancer-specific mortality, HR was 1.70 (95%CI, 1.01-2.85; P=0.047) (16).

Progression-free survival

In teo studies including 458 patients, sarcopenia occurred in 225 of 458 (49.1%) patients. No significant discrepancy of PFS was revealed (HR=1.56, 95%CI, 0.69-3.50, P=0.282, I^2=71.7%; Figure-3).

Sensitivity analyses and publication bias

Because of the small number of enrolled studies, we only performed the sensitivity analysis based on OS. After sequentially removing each study, we did not observe relatively change and the trend of results did not alter, which indicated the stability of our pooled results (Figure-4). And we did not observe the publication bias of OS according to Egger's test (P=0.094, Figure-5A) and Begg's test (P=0.462, Figure-5B).

Subgroup Analysis

A few studies were enrolled in the final quantitative analysis, so we only conducted a subgroup analysis for OS stratified by regions and stages. In patients from Asia, sarcopenia was associated with a poor OS (HR=2.49; 95%CI, 1.27-4.87, Figure-6A). Similarly, there was a significant difference in OS between westerners with or without sarcopenia (HR=1.65; 95%CI, 1.23-2.22; Figure-6A). For patients with localized or advanced/metastatic diseases, sarcopenia was also considered as a prognostic factor (HR=1.48, 95%CI 1.01-2.15; HR=2.14, 95%CI 1.45-3.15; respectively, Figure-6B).

DISCUSSION

Body composition is an increasingly important prognostic factor in many illnesses, such as chronic diseases, the elderly population as well as several malignancies (15, 26, 27). Several imaging techniques have been applied to evaluate the muscle mass including computed tomographic (CT) images, magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DEXA) (28). For patients with malignancies, CT images are commonly considered as a tool for staging, follo-

Figure 3 - Meta-analysis of the association between sarcopenia and PFS in patients with RCC.

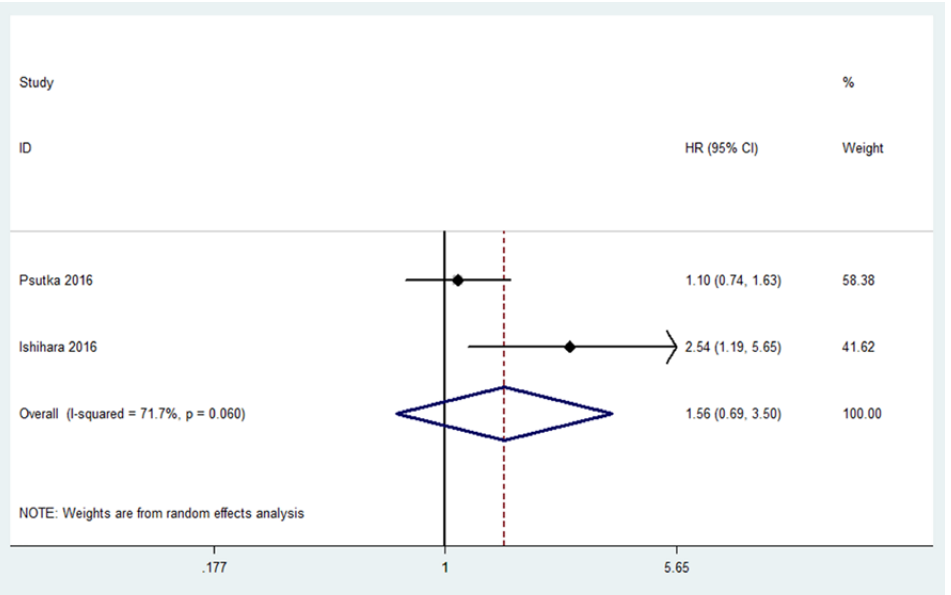
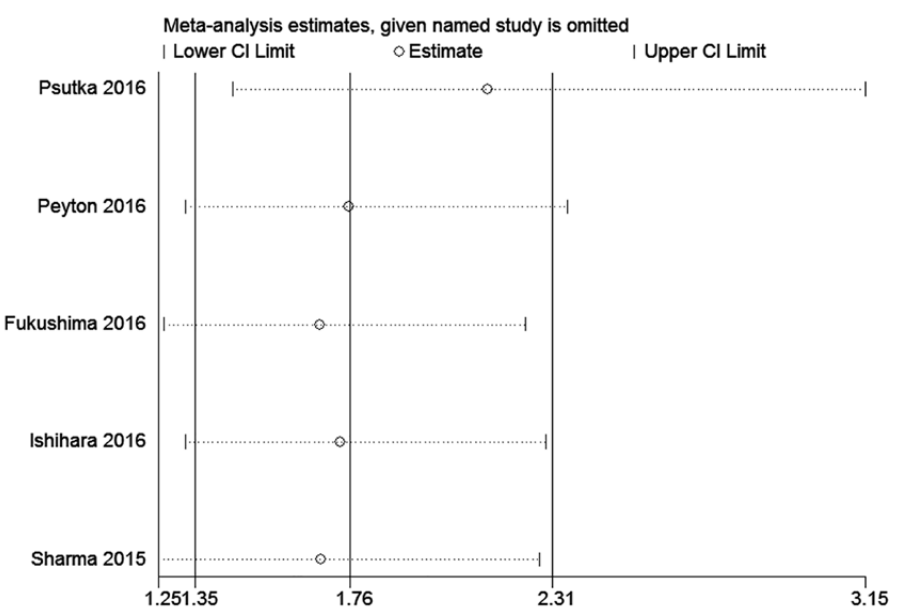


Figure 4 - Sensitivity analysis of OS.



wing up and surveillance. Furthermore, it could be served as a method for identifying sarcopenia. Sarcopenia is the age-related decline in skeletal muscle mass concomitant with impaired strength and/or function, which is highly prevalent in patients with cancers (27, 28). Besides, sarcopenia is associated with the prognosis of patients with RCC, but the results are mixed (16-19, 25). In consequence, we performed this meta-analysis to evaluate the prognostic value of sarcopenia in pa-

Figure 5 - Publication bias of OS: A: Egger's test; B: Begg's test.

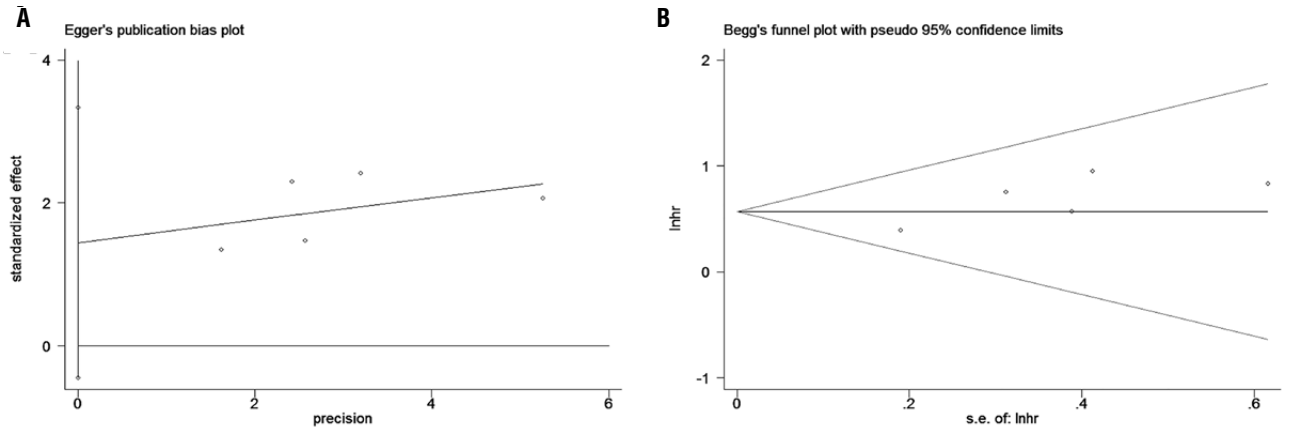
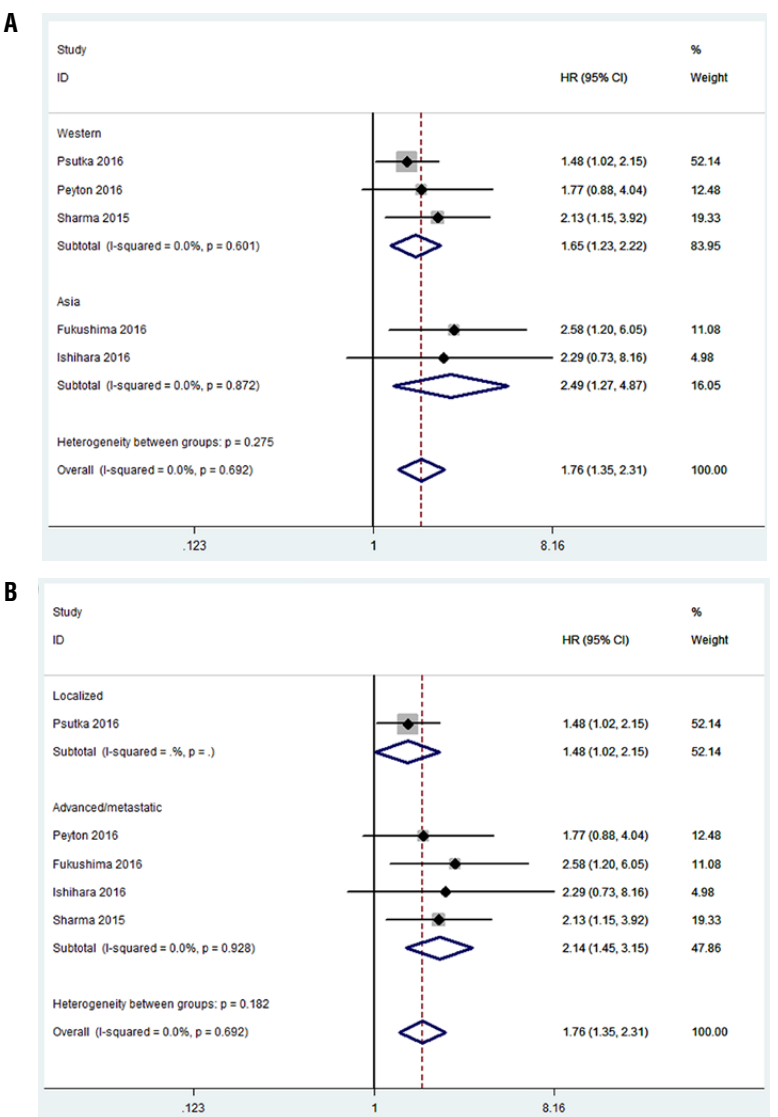


Figure 6 - Subgroup analyses of OS: A: stratified by regions; B: stratified by stages.



tients with RCC. In our study, we enrolled 5 studies incorporating 771 patients with RCC. We observed sarcopenia is associated with poor OS (HR=1.76; 95%CI, 1.35-2.31; P <0.001), while there was no significant discrepancy of PFS between patients with or without sarcopenia (HR=1.56, 95%CI, 0.69-3.50, P=0.282). Furthermore, when stratified by regions and stages, sarcopenia also serves as a predictive factor for OS in different subgroups. We did not detect publication bias, which indicated the robustness.

Reportedly, sarcopenia is associated with postoperative complications, dose-limiting toxicity and poor survival in patients with malignancies involving hepatocellular carcinoma, gastroesophageal tumor, colorectal cancer and urothelial carcinomas (14, 15, 29). For short-term outcomes, in patients with metastatic RCC, diminished muscle mass was found to be a significant predictor of toxicity (30). Peyton et al. also found that sarcopenia was associated with an increased risk of major complications in patients with stage III and IV kidney cancer (P=0.03) (25). While, as for long--term outcome, the prognostic value of sarcopenia in patients with RCC remains unclear. Auclin et al. used skeletal muscle index (SMI) to identify sarcopenia and observed that sarcopenia was not associated with OS in patients with metastatic RCC (did not report data) (31). Ishihara et al. also identified sarcopenia by SMI and also did not find the association between OS and sarcopenia in patients with metastatic RCC (HR 2.29, P=0.157) (19). In contrast, Fukushima et al. and Sharma et al. used SMI to define sarcopenia and revealed that sarcopenia is associated with poor OS in patients with metastatic RCC (HR 2.58, P=0.015; HR 2.13, P=0.016; respectively) (17, 18). For localized RCC, Psutka et al. demonstrated that sarcopenia is correlated to decreased CSS (HR 1.70, P=0.047) and OS (HR 1.48, P=0.039) (16). Besides, there is evidence that obesity may not be related to a worse prognosis unless it occurs concomitant to sarcopenia (sarcopenic obesity) (32). After pooling these pieces of evidence together, we found that sarcopenia is associated with poor OS in patients with RCC. In patients with localized and advanced/metastatic RCC, the results are consistent with previous results. As for disease progression, the relevant studies are few and the predictive value of sarcopenia remains unclear. Psutka et al. observed that sarcopenia is not associated with PFS (HR 1.10, P=0.65) in patients with localized RCC (16). While in patients with metastatic RCC, Ishihara et al. detected a significant association between sarcopenia and poor PFS (HR 2.54, P=0.016) (19). We pooled these results and observed that sarcopenia had no significant impact on PFS. The small number of enrolled studies and heterogeneity among studies existed, which may have affected the final results. If given more relevant studies and cases, we believe the difference of PFS between patients with or without sarcopenia might be observed.

The detailed interaction between sarcopenia and poor survival in patients with cancer remains indistinct. In patients with advanced/metastatic cancers, the poor survival may be associated with higher toxicity rates and poor response of treatments, so it seems possible that patients with sarcopenia may reduce the dose and be less likely to receive and complete treatments (30, 31). Sarcopenia is the result of a combination of decreased protein synthesis and increased protein degradation, and the increased protein is induced by the catabolic driver including systematic inflammation (33). Some studies have suggested sarcopenia is associated with higher levels of CRP and hypoalbuminemia, which were shown to be prognostic factors for RCC (19, 34). Besides, skeletal muscle is that muscle is a secretory organ of cytokines and other peptides (interleukin-6 [IL-6], IL-8, and leukemia inhibitory factor), which are extensively involved in inflammation processes (35). Furthermore, during the development of sarcopenia, oxidative pathways are also altered in skeletal muscle, which results in decreased ATP synthesis and uncoupling (36). Hence, sarcopenia is commonly accompanied by malnutrition and impaired immune response. Both the systematic immune response and nutrition decline may influence the treatment intolerance and response (37). Further, more relevant studies are required to explore the interaction between sarcopenia and RCC.

Performance status, which reflects the general health status of patients, is widely used for predicting the prognosis of patients with RCC (3, 4). However, it is evaluated by physicians, thus

its evaluation may be subjective and inconsistent. Sarcopenia reflects not only the skeletal muscle mass depletion on imaging but also a poor general health status (13, 27, 28). Besides, sarcopenia is more objective and defined based on imaging. CT scans are commonly used for staging and follow-up of patients, which is convenient to identify sarcopenia. Although, CT scan is an easy and objective method to assess muscle mass, muscle strength, and physical performance are also considered for sarcopenia diagnosis, and are not contemplated by CT scan.

Our study highlights the prognostic value of sarcopenia in patients with RCC. Therefore, the treatment options, close postoperative follow-up, and appropriate adjuvant treatments might be more emphasized for RCC patients with sarcopenia. Besides, we could provide the patients with suggestions to prevent and decrease the rates of sarcopenia, including physical exercise, vitamin D or omega-3 fatty acid dietary supplementation and others (27, 38).

Our study has several limitations. Firstly, only 5 studies involving 771 patients were included, which may limit the power of pooled results. And only 2 studies revealed the PFS, while only one study demonstrated the CSS. Secondly, all studies are retrospective, increasing the risk of bias. Next, the differences in characteristics between studies could also affect the validity of our results. So we conducted subgroup analyses based on available information. Finally, the methods of identifying sarcopenia are different. For instance, some studies measured SMI at L3 while others only measured the total psoas area and the cut-off values for defining sarcopenia are slightly different. Therefore, to better evaluate the prognostic value of sarcopenia in patients with RCC, a consensus for identifying sarcopenia should be made.

CONCLUSIONS

We carried out this meta-analysis to evaluate the prognostic value of sarcopenia in patients with RCC. We observed that patients with sarcopenia had a worse OS compared with those without sarcopenia in RCC. Larger, preferably prospective studies, are needed to confirm and update our findings.

ACKNOWLEDGEMENT

Xu Hu, Du-Wu Liao, Zhi-Qiang Yang, these authors contributed equally to this article.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
3. Motzer RJ, Jonasch E, Agarwal N, Bhayani S, Bro WP, Chang SS, et al. Kidney Cancer, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15:804-834.
4. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67:913-24.
5. Brookman-May SD, May M, Shariat SF, Novara G, Zigeuner R, Cindolo L, et al. Time to recurrence is a significant predictor of cancer-specific survival after recurrence in patients with recurrent renal cell carcinoma--results from a comprehensive multi-centre database (CORONA/SATURN-Project). BJU Int. 2013;112:909-16.
6. Klatte T, Ficarra V, Gratzke C, Kaouk J, Kutikov A, Macchi V, et al. A Literature Review of Renal Surgical Anatomy and Surgical Strategies for Partial Nephrectomy. Eur Urol. 2015;68:980-92.
7. Hu H, Yao X, Xie X, Wu X, Zheng C, Xia W, et al. Prognostic value of preoperative NLR, dNLR, PLR and CRP in surgical renal cell carcinoma patients. World J Urol. 2017;35:261-270.
8. Semeniuk-Wojtaś A, Lubas A, Stec R, Syryło T, Niemczyk S, Szczylik C. Neutrophil-to-lymphocyte Ratio, Platelet-to-lymphocyte Ratio, and C-reactive Protein as New and Simple Prognostic Factors in Patients With Metastatic Renal Cell Cancer Treated With Tyrosine Kinase Inhibitors: A Systemic Review and Meta-analysis. Clin Genitourin Cancer. 2018;16:e685-e693.

9. Shim SR, Kim SJ, Kim SI, Cho DS. Prognostic value of the Glasgow Prognostic Score in renal cell carcinoma: a meta-analysis. World J Urol. 2017;35:771-780.
10. Tsivian E, Tsivian M, Sze C, Schulman A, Polascik TJ. Clinicopathological characteristics of surgically treated localized renal masses in patients previously exposed to chemotherapy. Int Braz J Urol. 2019;45:332-339.
11. Semeniuk-Wojtaś A, Lubas A, Stec R, Syryło T, Niemczyk S, Szczylik C. Neutrophil-to-lymphocyte Ratio, Platelet-to-lymphocyte Ratio, and C-reactive Protein as New and Simple Prognostic Factors in Patients With Metastatic Renal Cell Cancer Treated With Tyrosine Kinase Inhibitors: A Systemic Review and Meta-analysis. Clin Genitourin Cancer. 2018;16:e685-e693.
12. Blum D, Stene GB, Solheim TS, Fayers P, Hjermstad MJ, Baracos VE, et al. Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification model--a study based on data from an international multicentre project (EPCRC-CSA). Ann Oncol. 2014;25:1635-42.
13. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31:1539-47.
14. Psutka SP, Carrasco A, Schmit GD, Moynagh MR, Boorjian SA, Frank I, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. Cancer. 2014;120:2910-8.
15. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer. 2016;57:58-67.
16. Psutka SP, Boorjian SA, Moynagh MR, Schmit GD, Costello BA, Thompson RH, et al. Decreased Skeletal Muscle Mass is Associated with an Increased Risk of Mortality after Radical Nephrectomy for Localized Renal Cell Cancer. J Urol. 2016;195:270-6.
17. Sharma P, Zargar-Shoshtari K, Caracciolo JT, Fishman M, Poch MA, Pow-Sang J, et al. Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Urol Oncol. 2015;33:339.e17-23.
18. Fukushima H, Nakanishi Y, Kataoka M, Tobisu K, Koga F. Prognostic Significance of Sarcopenia in Patients with Metastatic Renal Cell Carcinoma. J Urol. 2016;195:26-32.
19. Ishihara H, Kondo T, Omae K, Takagi T, Iizuka J, Kobayashi H, et al. Sarcopenia and the Modified Glasgow Prognostic Score are Significant Predictors of Survival Among Patients with Metastatic Renal Cell Carcinoma Who are Receiving First-Line Sunitinib Treatment. Target Oncol. 2016;11:605-617.
20. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
21. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
22. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
24. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56:455-63.
25. Peyton CC, Heavner MG, Rague JT, Krane LS, Hemal AK. Does Sarcopenia Impact Complications and Overall Survival in Patients Undergoing Radical Nephrectomy for Stage III and IV Kidney Cancer? J Endourol. 2016;30:229-36.
26. Carrero JJ, Johansen KL, Lindholm B, Stenvinkel P, Cuppari L, Avesani CM. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. Kidney Int. 2016;90:53-66.
27. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, et al. Sarcopenia: an overview. Aging Clin Exp Res. 2017;29:11-17.
28. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-23.
29. Pamoukdjian F, Bouillet T, Lévy V, Soussan M, Zelek L, Paillaud E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. Clin Nutr. 2018;37:1101-1113.
30. Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Ann Oncol. 2010;21:1594-8.

31. Zappala SM, Dong Y. Re: Russo GI, Regis F, Castelli T, et al. A Systematic Review and Meta-analysis of the Diagnostic Accuracy of Prostate Health Index and 4-kallikrein Panel Score in Predicting Overall and High-grade Prostate Cancer. Clin Genitourin Cancer 2017; 15:429-39. Clin Genitourin Cancer. 2017.
32. Watanabe D, Horiguchi A, Tasaki S, Kuroda K, Sato A, Asakuma J, et al. Impact of body mass index on clinicopathological outcomes in patients with renal cell carcinoma without anorexia-cachexia syndrome. Mol Clin Oncol. 2018;8:47-53.
33. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012;16:153-66.
34. Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med. 2006;119:526.e9-17.
35. Pratesi A, Tarantini F, Di Bari M. Skeletal muscle: an endocrine organ. Clin Cases Miner Bone Metab. 2013;10:11-4.
36. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cachexia and sarcopenia: mechanisms and potential targets for intervention. Curr Opin Pharmacol. 2015;22:100-6.
37. Bromwich E, McMillan DC, Lamb GW, Vasey PA, Aitchison M. The systemic inflammatory response, performance status and survival in patients undergoing alpha-interferon treatment for advanced renal cancer. Br J Cancer. 2004;91:1236-8.
38. Kung T, Springer J, Doehner W, Anker SD, von Haehling S. Novel treatment approaches to cachexia and sarcopenia: highlights from the 5th Cachexia Conference. Expert Opin Investig Drugs. 2010;19:579-85.

Correspondence address:
Xiang Li, MD
Department of Urology
West China Hospital, West China Medical School,
Sichuan University
37 Guoxue Street, Chengdu
610041, People's Republic of China
E-mail: hx_uro@sina.com

ORIGINAL ARTICLE

Vol. 46 (5): 716-724, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0331

The effects of menopause on the quality of life and long-term outcomes of transobturator tape treatment in women with stres urinary incontinence

Mehmet Oguz Sahin [1], Volkan Sen [1], Bora Irer [2], Guner Yildiz [3]

[1] Department of Urology, Manisa State Hospital, Manisa, Turkey; [2] Department of Urology, Izmir Metropolitan Municipality Esrefpasa Hospital, Izmir, Turkey; [3] Department of Urology, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Izmir, Turkey

ABSTRACT

Purpose: We aimed to investigate the effects of menopause on long-term outcomes of transobturator tape (TOT) surgery.

Materials and Methods: Patients who underwent TOT surgery were evaluated under two groups as postmenopausal and premenopausal. The International Consultation on Incontinence short-form questionnaire (ICIQ-SF), Incontinence Impact Questionnaire (IIQ-7) and Urogenital Distress Inventory-Short Form (UDI-6) questionnaires were completed by the patients at the 1st and 5th-year follow-up sessions. Patients with a postoperative UDI-6 and IIQ-7 score of <10 were considered as cured, those with lower postoperative scores compared to the preoperative period were regarded as improved, and the cases that had higher postoperative scores than preoperative values were interpreted as TOT failure. The TOT success rates were compared between the results obtained from UDI-6 and IIQ-7.

Results: A total of 109 patients were included in the study (53 postmenopausal and 56 premenopausal). We contacted with 90 (48 premenopausal and 42 postmenopausal) women at 1st year control and 80 (44 premenopausal and 36 postmenopausal) women at 5th year control. There was a significant improvement in all of three questionnaires between the preoperative and post-operative 1st year control (ICIQ-SF: 15.5±2.5 vs. 1.8±4.3, p <0.001; IIQ-7: 68.9±9.8 vs. 2.75±15.2, p <0.001; UDI-6: 27.1±11.1 vs. 6.0±14.6, p <0.001) and the preoperative and post-operative 5th year control (ICIQ-SF: 15.5±2.5 vs. 3.1±5.3, p <0.001; IIQ-7: 68.9±9.8 vs. 9.6±26.7, p <0.001; UDI-6: 27.1±11.1 vs. 5.1±10.0, p <0.001). When we compared the premenopausal and postmenopausal patients in terms of recurrent urinary tract infection (UTI); 5 (12%) patients had recurrent UTI in postmenopausal group but no patients had recurrent UTI in premenopausal group at 1st year follow-up (p=0.039) and similarly the same 5 (13.9%) patients in follow-up had recurrent UTI in postmenopausal group but no patients had recurrent UTI in premenopausal group at 5th year follow-up (p=0.045). There were no significant differences between the premenopausal and postmenopausal patients in terms of TOT success rates at 1st and 5th year control, evaluated with UDI-6 (1st year: p=0.198 and 5th year: p=0.687) and IIQ-7 (1st year: p=0.489 and 5th year: p=0.608) questionnaires.

Conclusions: Transobturator tape surgery is an effective and reliable method according to the long-term outcomes reported in this paper. In the current study, we determined that the TOT success rates were not affected by the presence of menopause.

ARTICLE INFO

Mehmet Oguz Sahin
http://orcid.org/0000-0002-1985-9312

Keywords:
Menopause; Urinary Incontinence, Stress; Quality of Life

Int Braz J Urol. 2020; 46: 716-24

Submitted for publication:
May 17, 2019

Accepted after revision:
October 13, 2019

Published as Ahead of Print:
April 01, 2020

INTRODUCTION

Urinary incontinence (UI) has been defined as involuntary urine loss by the International Continence Society (ICS) (1). Risk factors for UI include age, obesity and excess adipose tissue, parity, pregnancy, hormone replacement therapy for menopause, ethnicity and race, hysterectomy, dietary factors, socioeconomic status, smoking, physical activity, and comorbidities (diabetes, urinary tract infection (UTI), cognitive disorder, ischemic heart disease, physical disorders, and depression) (1, 2). Stress urinary incontinence (SUI), one of the most common types of UI, occurs when the bladder pressure exceeds urethral resistance due to increased abdominal pressure in exercise, sneezing, or coughing, and its prevalence ranges from 4 to 35% in the literature (3, 4). Transobturator tape (TOT) treatment was first described in 2001 and presents as an alternative to the mid-urethral sling technique, in which the synthetic mesh is inserted through the obturator foramen (5).

With menopause and advancing age, all urogynecologic disorders have been shown to increase. Menopause results in the reduction of the maximal urethral closure pressure. At the same time, bladder capacity and detrusor pressure during voiding is significantly decreased in the elderly population (6). On the other hand, estrogen receptors have been identified along the pelvic floor trigone and uterosacral ligaments including the urethra, vagina and bladder, and estrogen loss was often associated with urogenital atrophy and urinary symptoms after menopause (7). Stress urinary incontinence is more commonly seen among postmenopausal patients, and studies in the literature have reported different results in term of the success and complication rates of TOT surgery in premenopausal and postmenopausal patients (8, 9).

In this study, we aimed to investigate the effects of menopause on the long-term outcomes of the TOT operation, which is defined as a minimally invasive technique.

MATERIALS AND METHODS

After obtaining the approval of the local ethics committee, patients who underwent suburethral vaginal TOT surgery due to SUI in our urology clinic between January 2008 and June 2013 were retrospectively reviewed. Patients were evaluated under two groups as postmenopausal and premenopausal before the TOT operation. Life style changes including weight loss and pelvic muscle exercises were offered before and after the TOT surgery. Demographic characteristics of the patients, International Consultation on Incontinence short-form questionnaire (ICIQ-SF), Urogenital Distress Inventory-Short Form (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) questionnaire results, examination findings, stress test (MMK: Marshall-Marchetti-Krantz), Q-tip test, operation results, and complications were noted. Patients who previously had surgery for UI or pelvic organ prolapse, those having a marked neurological disease, urgency urinary incontinence (UUI), or cystocele or rectocele at the degree that would require surgical repair, and those who were using medication that made them prone to bleeding and the patients who were premenopausal before the surgery and then became menopausal during the time interval of study were excluded from the study. None of the patients with menopause took any hormonal therapy in their follow-up. TOT operation decision was scheduled for patients that had no preoperative pathology according to the urodynamic testing, a Q-tip test result of >30 degrees, and a positive stress test result. All operations were performed using the outside-in method under spinal anesthesia. Polypropylene mesh (Unitape T-Promedon®) was used as the TOT material during the operation. Cystoscopy was not routinely performed to all patients.

Urogynecologic examinations were performed on the patients. Q-tip angle, MMK test, operation success, and per-operative complications were recorded. The Turkish versions of the ICIQ-SF, IIQ-7 and UDI-6 questionnaires, which had been previously validated, were completed by the patients again at the first- and fifth-year follow-up sessions (10, 11). The outcomes of the operation were classified according to the subjective evaluations of the patients through the questionnaires: Patients with a postoperative UDI-6 and IIQ-7 score of <10 were considered as cured, those with lower postoperative scores compared to

the preoperative period were regarded as improved, and the cases that had higher postoperative scores than preoperative values were interpreted as TOT failure (12). The overall success rate of TOT was defined as sum of the cure and improvement rates. TOT success rates were compared between the groups at 1st and 5th year outcomes.

Data were analyzed using the Statistical Package for Social Sciences (SPSS, Inc., Chicago IL) version 22 and expressed as mean±standard deviation, number (n) and percentage (%) values. In the comparison of categorical variables between the groups, the X^2 test and Student's t-test were employed to compare continuous variables. A p value of 0.05 was considered to be statistically significant.

RESULTS

A total of 109 patients were included in the study and their mean age was 52.4±10.1 (27-76) years. There were 53 postmenopausal (48.6%) and 56 premenopausal (51.4%) women. The mean body mass index (BMI) of the patients was 26.2±4.0 (20.2-34.4) kg/m^2. The mean Q-tip test angle was 57.0±17.1 (30-90) degrees and the mean follow-up period was 74.4±46.2 (1-138) months. The mean operation time was 29.7±9.7 (12-60) minutes, and the mean hospitalization time was 1.2±0.5 (1-3) days. For all patients, the cough (MMK) test was positive and UUI was negative. We contacted with 90 (48 premenopausal and 42 postmenopausal) women at 1st year control and 80 (44 premenopausal and 36 postmenopausal) women at 5th year control (Figure-1).

The overall success rate of TOT procedure was detected as 93.3% at 1st year follow-up and 88.8% at 5th year follow-up according to both IIQ-7 and UDI-6 questionnaires. There was no significant difference between the success rates of premenopausal and postmenopausal patients at 1st year follow-up (93.7% vs. 92.9%, p=0.865) and 5th year follow-up (90.9% vs. 86.1%, p=0.499) (Table-1). The cure rates were also similar between the premenopausal and postmenopausal patients

Figure 1 - The first-year and fifth-year distribution of the patients that underwent TOT surgery.

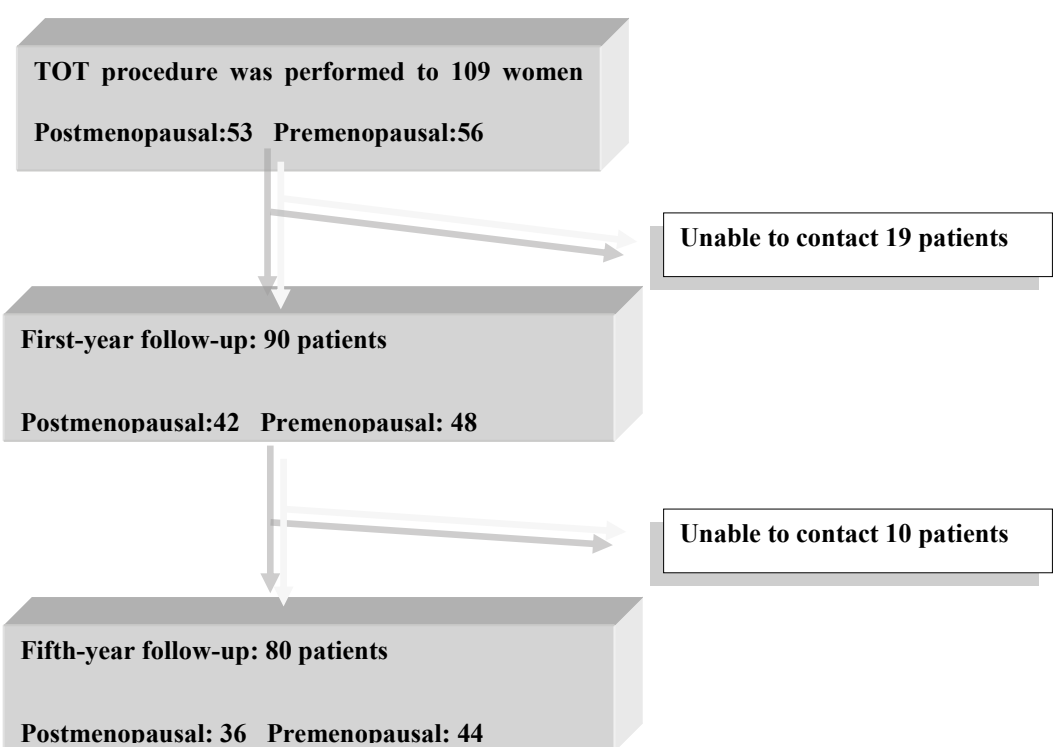


Table 1 - Comparison of the cure and success rates of postmenopausal and premenopausal groups in terms of the first-year and fifth-year outcomes according to IIQ7 and UDI-6.

	Postoperative 1st year (90 patients; 48 premenopausal, 42 postmenopausal)						Postoperative 5th year (80 patients; 44 premenopausal, 36 postmenopausal)					
IIQ-7	Failure	Cure	P*	Improvement	Success	P**	Failure	Cure	P*	Improvement	Success	P**
	6 (6.7%)	73 (81.1%)		11 (12.2%)	84 (93.3%)		9 (11.2%)	58 (72.5%)		13 (16.3%)	71 (88.8%)	
Postmenopausal	3 (7.1%)	33 (78.6%)		6 (14.3%)	39 (92.9%)		5 (13.9%)	25 (69.4%)		6 (16.7%)	31 (86.1%)	
Premenopausal	3 (6.3%)	40 (83.3%)	0.821	5 (10.4%)	45 (93.7%)	0.865	4 (9.1%)	33 (75.0%)	0.485	7 (15.9%)	40 (90.9%)	0.499
	Failure	Cure	P*	Improvement	Success	P**	Failure	Cure	P*	Improvement	Success	P**
UDI-6	6 (6.7%)	57 (63.3%)		27 (30.0%)	84 (93.3%)		9 (11.2%)	58 (72.5%)		13 (16.3%)	71 (88.8%)	
Postmenopausal	3 (7.1%)	23 (54.8%)		16 (38.1%)	39 (92.9%)		5 (55.6%)	25 (69.4%)		6 (16.7%)	31 (86.1%)	
Premenopausal	3 (6.3%)	34 (70.8%)	0.648	11 (22.9%)	45 (93.7%)	0.865	4 (44.4%)	33 (75.0%)	0.485	7 (15.9%)	40 (90.9%)	0.499

IIQ-7 = Incontinence Impact Questionnaire; **UDI-6**: Urogenital Distress Inventory-Short Form.
***** = Chi-square test; p values show the comparison of the premenopausal and postmenopausal patients according to failure and cure rates.
****** = Chi-square test; p values show the comparison of the premenopausal and postmenopausal patients according to failure and success rates.

according to IIQ-7 (83.3% vs. 78.6%, p=0.821) and UDI-6 (70.8% vs. 54.8%, p=0.648) at 1st year; IIQ-7 (75.0% vs. 69.4%, p=0.485) and UDI-6 (75.0% vs. 69.4%, p=0.485) at 5th year follow-up (Table-1).

When we compared the premenopausal and postmenopausal patients in terms of recurrent urinary tract infection (UTI); 5 (12%) patients had recurrent UTI in postmenopausal group but no patients had recurrent UTI in premenopausal group at 1st year follow-up (p=0.039) and similarly the same 5 (13.9%) patients on follow-up had recurrent UTI in postmenopausal group but no patients had recurrent UTI in premenopausal group at 5th year follow-up (p=0.045). No new recurrent UTI was added between 1st and 5th year follow-up. While 22 (20.2%) women had urgency in the preoperative period, the postoperative new urgency was observed in three patients (3.3%) in 1st year and 11 patients (13.8%) in 5th year. In addition, no UUI was found in the preoperative period whereas UUI was observed to newly develop in five patients (5.6%) in the first-year and 11 (13.8%) patients in the fifth-year follow-up.

There was a significant improvement in all of the three questionnaires between the preoperative and post-operative 1st year control (ICIQ-SF: 15.5±2.5 vs. 1.8±4.3, p <0.001; IIQ-7: 68.9±9.8 vs. 2.75±15.2, p <0.001; UDI-6: 27.1±11.1 vs. 6.0±14.6, p <0.001) and the preoperative and post-operative 5th year control (ICIQ-SF: 15.5±2.5 vs. 3.1±5.3, p <0.001; IIQ-7: 68.9±9.8 vs. 9.6±26.7, p <0.001; UDI-6: 27.1±11.1 vs. 5.1±10.0, p <0.001). The preoperative Q-tip test angles were significantly lower in the postoperative 1st and 5th years (p <0.001), which is an indication of the efficacy and permanence of the positive outcomes of the operation (Table-2).

There was no significant difference between the postmenopausal and premenopausal patients in terms of BMI, Q-tip angle, follow-up duration, operation time, and hospitalization time according to the evaluations undertaken in the 1st and 5th years (p >0.05) (Table-3). Three postmenopausal and two premenopausal women had a positive result in the cough test in the 1st year, with no statistically significant difference (p=0.564). At

Table 2 - The comparison of the questionnaires scores, UI symptoms and physical examination results of patients according the follow - up years (preoperative vs postoperative 1st year and preoperative vs postoperative 5th year).

	Preoperative (n=109)	Postoperative 1st year (n=90)	Postoperative 5th year (n=80)	P*
MMK test	0 (0%)	85 (94.4%)	73 (91.3%)	<0.001
Q tip (°)	57.0±17.1	17.1±12.5	19.8±15.9	<0.001
SUI symptoms	109 (100%)	6 (6.7%)	9 (11,3%)	<0.001
De-novo UUI	-	5 (5.6%)	11 (13.8%)	-
ICIQ-SF	15.5±2.5	1.8±4.3	3.1±5.3	<0.001
IIQ-7	68.9±9.8	2.75±15.2	9.6±26.7	<0.001
UDI-6	27.1±11.1	6.0±14.6	5.1±10.0	<0.001

MMK = Marshall-Marchetti-Krantz; **SUI** = Stress urinary incontinence; **UUI** = Urge urinary incontinence; **ICIQ-SF** = International Consultation on Incontinence short-form questionnaire; **IIQ-7** = Incontinence Impact Questionnaire; **UDI-6** = Urogenital Distress Inventory-Short Form.

*= p values show both of the comparison of preoperative vs postoperative 1st year and preoperative vs postoperative 5th year outcomes.

5th year of follow-up, premenopausal group had 3 patients with positive cough test, while post-menopausal group had four. The difference was not significant (p=0.419). Concerning systemic diseases, there was no difference between the 1st year and 5th year results of the groups (p=0.734 and p=0.838, respectively) (Table-3).

There was no significant difference between the postmenopausal and premenopausal groups in terms of the 1st and 5th year complication rates (p=0.156 and p=0.172, respectively). In the peroperative period, four women (3.7%) had bleeding that resulted in a blood loss of greater than 200mL and only one (0.9%) required erythrocyte suspension transfusion. All four patients were premenopausal. Bladder injuries were found in two (1.8%) women; thus, for these cases, the catheter was withdrawn seven days later and the treatment was initiated. Both these patients were postmenopausal. Except for two women with bladder injuries, all catheters were withdrawn on the first postoperative day.

In the early postoperative period, two patients had acute urinary retention (AUR), and kept the urinary catheter for 7 days. They had no other issues during follow-up. Both women that developed AUR were in the premenopausal group. Among the late postoperative complications evaluated, there was no difference between the postmenopausal and premenopausal groups in terms of de novo urgency, de novo UUI, dyspareunia, perineal pain, and vaginal discharge in 1st and 5th year follow-ups (p >0.05) (Table-3).

DISCUSSION

Urinary incontinence constitutes an important sociocultural health problem with high prevalence. Considering that the quality of life has attained more importance and the average life expectancy has extended, SUI treatment will become more valuable in the coming years with the increased number of geriatric individuals.

Studies showing the effects of menopause on various surgical techniques applied in the treatment of SUI report different results. While some emphasize the negative effects of menopause, others suggest that there is no such effect. In 2010, Rechberger et al. concluded that both menopause and aging had a detrimental effect on the ultimate outcome of both retropubic and transobturator sling due to the development of textural and hormonal changes (13). The study undertaken by Polat et al. confirms this finding, they found no significant difference in the mean operation time, length of hospital stay or intraoperative and postoperative complications, but noted that the premenopausal women were more satisfied with

Table 3 - Comparison of the demographic characteristics, surgical outcomes and complications of the postmenopausal and premenopausal groups in terms of follow-up years.

	Postoperative 1.st year (n=90)			Postoperative 5.th year (n=80)		
	Premenopausal n=48 (53.3%)	Postmenopausal n=42 (46.7%)	P	Premenopausal n=44 (55%)	Postmenopausal n=36 (45%)	P
BMI (kg/m^2)	27.1±4.2	26.6±3.6	0.370	27.2±4.2	26.3±3.6	0.234
Follow-up time (months)	94.8±33.1	83.6±37.7	0.148	102.3±22.5	95.5±25.2	0.210
Operation time (min)	29.7±10.6	29.5±9.0	0.931	29.5±10.8	29.6±9.7	0.978
Hospitalization (days)	1.2±0.6	1.1±0.3	0.264	1.3±0.6	1.1±0.3	0.200
Co-morbidities						**0.838**
No	26 (54.2%)	27 (64.3%)	0.734	24 (54.5%)	22 (61.1%)	
Diabetes Mellitus	8 (16.7%)	5 (11.9%)		7 (15.9%)	5 (13.9%)	
Hypertension	5 (10.4%)	4 (9.5%)		5 (11.4%)	4 (11.1%)	
Thyroid diseases	3 (6.3%)	3 (7.1%)		2 (4.5%)	3 (8.3%)	
COPD	4 (8.3%)	1 (2.4%)		4 (9.1%)	1 (2.8%)	
Complications						**0.172**
No	42 (87.5%)	40 (95.2%)	0.156	40 (90.1%)	34 (94.4%)	
Bleeding	4 (8.3%)	0 (0.0%)		3 (6.8%)	0 (0.0%)	
Acute urinary retention	2 (4.2%)	0 (0.0%)		1 (2.3%)	0 (0.0%)	
Bladder injury	0 (0.0%)	2 (4.8%)		0 (0.0%)	2 (5.6%)	
MMK(+)	2 (4.2%)	3 (7.1%)	0.564	4 (9.1%)	3 (8.3%)	0.419
Q tip (°)	16.4±13.0	17.9±11.9	0.571	19.7±16.1	19.9±16.0	0.955
SUI (+)	3 (6.3%)	3 (7.1%)	0.542	4 (9.1%)	5 (13.9%)	0.319
De-novo urgency	2 (4.2%)	1 (2.4%)	0.550	5 (11.4%)	6 (16.7%)	0.344
De-novo urge incontinence	3 (6.3%)	2 (4.8%)	0.564	5 (11.4%)	6 (16.7%)	0.332
Recurrent UTI	0 (0.0%)	5 (12.0%)	0.039	0 (0.0%)	5 (13.9%)	0.045
Dyspareunia	6 (12.5%)	3 (7.1%)	0.314	5 (11.4%)	2 (5.6%)	0.307
UDI-6	7.1±13.0	10.7±18.1	0.274	9.8±16.8	12.8±19.8	0.453
IIQ-7	7.6±18.7	10.9±20.3	0.421	15.1±30.3	17.5±24.9	0.699
ICIQ-SF	1.8±4.6	1.8±4.0	0.984	2.9±5.9	3.3±4.8	0.776

BMI = Body mass index; **DM** = Diabetes Mellitus; **HT**: Hypertension; **COPD** = Chronic obstructive pulmonary disease; **MMK** = Marshall-Marchetti-Krantz; **SUI** = Stress urinary incontinence; **UTI**: Urinary tract infection; **UDI-6** = Urogenital Distress Inventory-Short Form; **IIQ-7** = Incontinence Impact Questionnaire; **ICIQ-SF** = International Consultation on Incontinence short-form questionnaire.

the surgery than the postmenopausal women. In addition, the improvement in the UDI-6 scores of premenopausal women was more significant (8). In contrast to these results, researchers investigating the effect of menopause on the success and failure rate of the Burch procedure examined 258 patients and observed no effect of menopause on the failure rate (14). Yasa et al. showed that TOT surgery in SUI treatment had high rates of success and patient satisfaction and a low postoperative morbidity rate in postmenopausal women aged over 65 years (15). Agarwal et al. reported that TOT surgery was more successful in premenopausal women younger than 50 years with a urethral mobility greater than 30 degrees (16). In the present study, there was no difference between the postmenopausal and premenopausal groups in terms of TOT success and fifth-year follow-up evaluations. We did not find any difference in the duration of follow-up, operation time, and hospitalization time between the two groups. According to the results of the UDI-6 and IIQ-7 questionnaires, the postmenopausal and premenopausal groups did not differ in relation to the rates of TOT failure, TOT success and clinical improvement.

Arrabal-Polo et al. calculated the total complication rate of TOT surgery as 12% in their study (17). Kaelin-Gambirasio et al. found the peroperative and early postoperative complication rate to be 9.5% (18). In our study, the peroperative and early postoperative complication rate being 7.2% confirms the safety of the TOT operation.

Richter et al. comparatively evaluated patients under 65 years (34.6% premenopausal) and over 65 years (all postmenopausal) that underwent the Burch colposuspension or pubovaginal sling for the treatment of SUI and found no difference in the complication rates (including hemorrhage) of the two groups (19). Yasa et al. did not observe any bladder perforation among the postmenopausal patients aged below and over 65 years that underwent TOT surgery due to SUI and noted no statistically significant difference between the groups concerning other complications observed, namely voiding dysfunction, vaginal erosion, de novo urgency, and suprapubic or hip pain (15). In the current study, considering the four patients with a blood loss of more than 200mL, the rate of hemorrhage was 2.8%.

Voiding difficulty is another complication that develops in the postoperative period. Urinary obstruction that occurs in the first few days may be due to edema and pain, but in the following days, specifically within 10 days, this effect is minimized and the patient is expected to perform the voiding function without difficulty (20). In the present study, transient urinary retention developed in two patients (1.8%) in the early postoperative period, and therefore the catheter remained for one week. The patients were able to spontaneously urinate after the catheter was removed. The four patients with hemorrhage and the two patients with acute urinary retention were in the premenopausal group. Bladder injury was seen in only two patients, both in the postmenopausal group. Despite the absence of a statistically significant difference between the two groups in terms of complications, the presence of hemorrhage in four and acute urinary obstruction in two premenopausal patients could be explained by congestion, blood supply and edema due to estrogen, and similarly, the two cases of bladder injury being seen in the postmenopausal group can be attributed to the reduced level of estrogen, resulting in tissue thinning and increased fragility.

Another condition that can be seen after TOT operations is de novo urgency incontinence, which was identified at a rate of 5.6% in the first year and 13.8% in the fifth year of the current study. Consistent with the report of Yasa et al., we found no difference between the postmenopausal and premenopausal groups (15).

Urinary tract infection, another complication encountered after mid-urethral sling operations, occurs at a rate of 34% in the first three months and 50% in the first year (21, 22). The prevalence of recurrent UTI is reported as 6.4% in various case series (23). In a study by Weintraub et al., the rate of UTI was found to be 21.3% after mid-urethral sling surgery. When the groups with and without infection were considered, the mean age of the infection group was greater, but without statistical significance. The menopause status was not different in these groups. The authors suggested that UTI had a linear relationship with the presence of perineal hematoma and prolonged hospitalization time (24). In our

patient groups, the rate of recurrent UTI was 5.6% in the first year and 6.3% in the fifth-year follow--up. All the patients presenting with recurrent UTI were in the postmenopausal group, and there was a statistically significant difference for the first-year and fifth-year values. As expected, the mean age of the postmenopausal group was higher than that of the premenopausal group. None of the patients with recurrent UTI had peroperative complications. We consider that the reason for detecting increased recurrent UTI in the postmenopausal group is the reduced estrogen, blood supply, and weakening of the bladder mucosal barrier.

The main limitation of this study is its retrospective design. Data about menopause status of patients was only evaluated before TOT surgery also there was no data which patients used hormonal therapy for menopause.

CONCLUSIONS

Transobturator tape surgery is an effective and reliable method according to the long-term outcomes reported in this paper. In the current study, we determined that the TOT success rates were not affected by the presence of menopause.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29:4-20.
2. Dumoulin C, Hunter KF, Moore K, Bradley CS, Burgio KL, Hagen S, et al. Conservative management for female urinary incontinence and pelvic organ prolapse review 2013: Summary of the 5th International Consultation on Incontinence. Neurourol Urodyn. 2016;35:15-20.
3. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21:167-78.
4. Staskin D, Kelleher C. Committee 5A initial assessment of urinary incontinence in adult male and female patients. In: Incontinence: 5th International Consultation on Incontinence, edited by P. Abrams, S. Khoury, A. J. Wein, and L. Cardozo. Paris: ICUD-EAU 2013;361–88.
5. Delorme E. [Transobturator urethral suspension: mini-invasive procedure in the treatment of stress urinary incontinence in women]. Prog Urol. 2001;11:1306-13.
6. Cardozo L, Rekers H, Tapp A, Barnick C, Shepherd A, Schussler B, et al. Oestriol in the treatment of postmenopausal urgency: a multicentre study. Maturitas. 1993;18:47-53.
7. Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. Urology. 2003;62(4 Suppl 1):45-51.
8. Dursun P, Bildaci TB, Zeyneloglu HB, Kuscu E, Ayhan A. Transobturator tape operation is more effective in premenopausal women than in postmenopausal women with stress incontinence. Korean J Urol. 2011;52:612-5.
9. Karatas A, Duran B, Ozlu T, Koc O, Donmez ME, Guler A. Evaluation of treatment success in patients undergoing transobturator tape surgery. J Turk Soc Obstet Gynecol. 2014;2:115-8.
10. Cetinel B, Ozkan B, Can G. The validation study of ICIQ-SF Turkish. Turk J Urol. 2004; 30: 332-8.
11. Cam C, Sakalli M, Ay P, Cam M, Karateke A. Validation of the short forms of the incontinence impact questionnaire (IIQ-7) and the urogenital distress inventory (UDI-6) in a Turkish population. Neurourol Urodyn. 2007;26:129-33.
12. Cañete P, Ortiz E, Domingo S, Cano A. Transobturator suburethral tape in the treatment of stress urinary incontinence: efficacy and quality of life after 5 year follow-up. Maturitas. 2013;74:166-71.
13. Rechberger T, Futyma K, Jankiewicz K, Adamiak A, Bogusiewicz M, Skorupski P. Body mass index does not influence the outcome of anti-incontinence surgery among women whereas menopausal status and ageing do: a randomised trial. Int Urogynecol J. 2010;21:801-6.
14. Sun MJ, Ng SC, Tsui KP, Chang NE, Lin KC, Chen GD. Are there any predictors for failed Burch colposuspension? Taiwan J Obstet Gynecol. 2006;45:33-8.
15. Yasa C, Gungor Ugurlucan F, Dural O, Yumru H, Gunaydin C, Yalcin O. Transobturator Tape Operation for the Treatment of Stress Urinary Incontinence in Postmenopausal Women Aged Over 65 Years. Low Urin Tract Symptoms. 2018;10:153-157.
16. Agarwal A, Patnaik P, Shaw D, Rathee V, Khan SW, Jain M, et al. Influence of Demographic and Clinical Factors on Surgical Outcomes of the Transobturator Tape Procedure in Patients with Stress Urinary Incontinence. Curr Urol. 2015;8:126-32.

17. Arrabal-Polo MÁ, Palao-Yago F, Zuluaga-Gómez A, López-León VM, Merino-Salas S, Lahoz-García C, et al. Complications from the placement of a tension-free suburethral sling using the transobturator and retropubic methods for treatment of female urinary incontinence. Urol Int. 2012;89:97-102.
18. Kaelin-Gambirasio I, Jacob S, Boulvain M, Dubuisson JB, Dällenbach P. Complications associated with transobturator sling procedures: analysis of 233 consecutive cases with a 27 months follow-up. BMC Womens Health. 2009;9:28.
19. Richter HE, Goode PS, Brubaker L, Zyczynski H, Stoddard AM, Dandreo KJ, et al. Two-year outcomes after surgery for stress urinary incontinence in older compared with younger women. Obstet Gynecol. 2008;112:621-9.
20. Zaragoza MR. Expanded indications for the pubovaginal sling: treatment of type 2 or 3 stress incontinence. J Urol. 1996;156:1620-2.
21. Anger JT, Litwin MS, Wang Q, Pashos CL, Rodríguez LV. Complications of sling surgery among female Medicare beneficiaries. Obstet Gynecol. 2007;109:707-14.
22. Suskind AM, Clemens JQ, Dunn RL, Zhang Y, Stoffel JT, Hollenbeck BK. Effectiveness of mesh compared with nonmesh sling surgery in Medicare beneficiaries. Obstet Gynecol. 2013;122:546-52.
23. Groutz A, Levin I, Gold R, Pauzner D, Lessing JB, Gordon D. "Inside-out" transobturator tension-free vaginal tape for management of occult stress urinary incontinence in women undergoing pelvic organ prolapse repair. Urology. 2010;76:1358-61.
24. Weintraub AY, Reuven Y, Paz-Levy D, Yohay Z, Idan I, Elharar D, et al. Prevalence and risk factors for urinary tract infection up to one year following midurethral sling incontinence surgery. Eur J Obstet Gynecol Reprod Biol. 2018;222:146-150.

Correspondence address:
Mehmet Oguz Sahin, MD
Department of Urology, Manisa State Hospital
Manisa, Turkey
Telephone: + 90 505 246-7376
E-mail: urologoguz@yahoo.com

ORIGINAL ARTICLE

Vol. 46 (5): 725-740, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0387

Effects of testicular dysgenesis syndrome components on testicular germ cell tumor prognosis and oncological outcomes

Ismail Selvi [1], Erdem Ozturk [2], Taha Numan Yikilmaz [2], Selcuk Sarikaya [3], Halil Basar [2]

[1] Department of Urology, Karabük University Training and Research Hospital, Karabük, Turkey; [2] Department of Urology, Health Science University Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey; [3] Department of Urology, Health Science University Gulhane Training and Research Hospital, Ankara, Turkey

ABSTRACT

Purpose: To evaluate whether components of Testicular Dysgenesis Syndrome (TDS) affect testicular germ cell tumor (TGCT) prognosis and oncological outcomes. According to the hypothesis called TDS; undescended testis, hypospadias, testicular cancer and spermatogenic disorders share the same risk factors and have a combined fetal origin. *Materials and Methods:* We retrospectively evaluated the stages and oncological outcomes of 69 patients who underwent radical orchiectomy between January 2010 and December 2014 due to TGCT in our department. The presence of undescended testis, hypospadias and semen parameters disorders were recorded according to anamnesis of patients. *Results:* Among 69 patients with TGCT, only 16 (23.1%) had TDS. Significantly higher rate of TDS (36.1% vs. 9.1%) was observed at the advanced stages of TGCT(p=0.008). In the TDS group, the rates of local recurrence (50% vs. 11.3%, p<0.001), distant metastasis (93.6% vs. 3.8%, p<0.001) and cancer-spesific mortality (87.5% vs. 3.8%, p<0.001) were found significantly higher than those without TDS. The predicted time for recurrence-free survival (13.70±5.13 vs. 100.96±2.83 months, p<0.001) metastasis-free survival (13.12±4.21 vs. 102.79±2.21 months, p <0.001) and cancer-specific survival (13.68±5.38 vs. 102.80±2.19 months, p<0.001) were also statistically lower in this group. *Conclusions:* According to our preliminary results, there is an apparent relationship between TDS and tumor prognosis. Even if the components of TDS alone did not contain poor prognostic features for TGCT, the presence of TDS was found as the most important independent predictive factor for oncological outcomes in both seminomas and nonseminomas as well as all patients with TGCT.

ARTICLE INFO

Ismail Selvi
http://orcid.org/0000-0003-3578-0732

Keywords:
Cryptorchidism; Testicular Germ Cell Tumor [Supplementary Concept]; Hypospadias

Int Braz J Urol. 2020; 46: 725-40

Submitted for publication:
June 11, 2019

Accepted after revision:
November 14, 2019

Published as Ahead of Print:
April 01, 2020

INTRODUCTION

Testicular dysgenesis syndrome (TDS) is one of the current topics that has been described in recent years. Undescended testis, hypospadias, decreased spermatogenesis and testicular germ cell tumor (TGCT) form TDS components (1). One or more of these disorders occur in about 1 in 6 young men in Northern Europe (2). TDS has a common fetal origin associated with deficiencies

in fetal androgen production (3). A failure in normal differentiation of fetal germ cells is effective in the formation of this syndrome. Increase in the incidence of TGCT in young men is also related to this mechanism. That is why TDS have been associated with TGCT (1). The hypotheses related to TDS have been strengthened by new studies since the last two decades (4, 5). Althought there are still controversial views about TDS, these studies have aimed to provide evidence verifying the reality of TDS based on a few key aspects, such as genetic factors, environmental endocrine-disrupting chemicals, lifestyle factors and intrauterine growth disorders (6, 7).

The biological mechanism of TDS was tried to be demonstrated in animal models due to limitations in human studies (4). Nevertheless, more evidence is needed to reinforce TDS hypothesis (8). According to the literature, semen analysis and testicular histology support the association between TGCT and TDS (9). But there is no detailed evaluation to show the effects of TDS components on TGCT prognosis. We aimed to evaluate whether components of TDS have an effect on TGCT prognosis and oncological outcomes.

MATERIALS AND METHODS

After obtaining the approval of the local ethics committee (protocol number: 77192459-050.99-E.2812, 3/19), we retrospectively evaluated the stages and oncological outcomes of 77 patients who underwent radical orchiectomy between January 2010 and December 2014 due to TGCT at our department. The presence of undescended testis, hypospadias, disorders of semen parameters and atrophic testis (testicular volume <12mL) were recorded. As our study also included non-married patients, it was not possible to evaluate the fertility status for all patients. Instead of this, disorders of semen parameters were examined. Demographic data, histological tumor types, clinical stages, tumor side, tumor sizes, expression of serum tumour markers (Alpha-fetoprotein, Beta human chorionic gonadotropin [β-hCG] and Lactate dehydrogenase [LDH]), prognostic factors in pathology specimen, post-orchiectomy follow-up period, presence of adjuvant therapy after orchiectomy, rates of local recurrence, distant metastasis and cancer-specific survival (CSS) were also recorded. 69 patients with complete data were included in the study. The patients whose data could not be completely collected were excluded from the study.

Tumor stages were recorded according to the 2009 classification of Tumor-Node-Metastasis. Patients were divided into two main groups. Stage IA and IB were determined as early stage (Group I). Stage IS, IIA/IIB/IIC and IIIA/IIIB/IIIC were determined as advanced stage (Group II).

The definition of TDS involves the presence of at least two of the following: undescended testis, hypospadias, decreased spermatogenesis and testicular germ cell tumor (4). As all patients had TGCT, those with any of undescended testis, hypospadias or disorders of semen parameters formed the TDS group. 16 patients with TDS and 53 patients without TDS were determined and a subgroup analysis was also done.

Pathological prognostic factors were based on the Guidelines of European Association of Urology on Testicular Tumors (9).The prognostic factors for the stage I seminomas were rete testis involvement and tumor size greater than 4cm.The presence of lymphovascular invasion (LVI), the percentage of embryonal carcinoma more than 50% and the proliferation rate above 70% were prognostic factors for stage I non-seminomas.

Statistical analysis

To compare the differences between the two groups, the normality status was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson Chi-square or Fisher exact analysis for categorical variables, Mann-Whitney U test for continuous variables in non-normal distribution were used. Kaplan-Meier was used for survival analysis and Cox regression analysis was used for determining the independent variables. The analyzes were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. $P < 0.05$ was considered statistically significant.

RESULTS

Median age of the 69 male patients was 31 (min:8-max:60). Demographic and clinical cha-

racteristics of the patients are shown in Tables 1 and 2. During the median follow-up period of 57 (6-106) months, the distant metastases were located at lung in 8 patients, liver in 4 patients and non-regional lymph nodes in 5 patients.

When the early and advanced tumor stages were compared, it was shown that the predicted time for recurrence-free survival (RFS) (71.61±8.02 vs. 96.57±4.65 months, p=0.01), metastasis-free survival (MFS) (68.32±7.91 vs. 96.99±4.43 months, p=0.003) and cancer-specific survival CSS (71.18±7.73 vs. 96.67±4.57 months, p=0.007) were statistically lower in patients with advanced stage (Figures 1A, 1B and 1C).

In a subgroup analysis, patients were classified in terms of the presence of TDS. Significantly higher TDS rates (36.1% vs. 9.1%) were observed in the advanced stages (p=0.008) (Table-2). In the TDS group, the rates of loctal recurrence (50% vs. 11.3%, p <0.001), distant metastasis (93.6% vs. 3.8%, p <0.001) and cancer-specific mortality (87.5% vs. 3.8%, p <0.001) were found significantly higher than those without TDS (Table-3). When patients with seminoma and non-seminoma were compared between themselves, in the presence of TDS, the rate of local recurrence (88.9% vs. 57.1%) was higher in non-seminomas, whereas distant metastasis (100% vs. 88.9%) and cancer-specific mortality rates (100% vs. 77.8%) were higher in seminomas (Table-3).

The predicted time for recurrence-free survival (RFS) (13.70±5.13 vs.100.96±2.83 months, p <0.001), metastasis-free survival (MFS) (13.12±4.21 vs. 102.79±2.21 months, p <0.001) and cancer-specific survival (CSS) (13.68±5.38 vs. 102.80±2.19 months, p <0.001) were statistically lower in patients with TDS (Figures 2A, 2B and 2C). In the presence of TDS, the predicted time for RFS was longer in patients with seminoma (13.64±4.56 vs.12.66±6.48 months, p <0.001). Conversely, the predicted time for MFS

Table 1 - Distribution of patients according to tumor stages, histologic tumor types, components of testicular dysgenesis syndrome and oncologic outcomes.

Stage	Number of seminoma patients	Number of non-seminoma patients	Number of mix germ cell tumor	History of undescended testis	History of hypospadiass	History of subfertility	Numbers of patients with testicular dysgenesis syndrome	Post-treatment recurrence and histological subtype	Presence of testicular dysgenesis syndrome in patients with recurrence	Post-treatment metastasis and histological subtype	Presence of testicular dysgenesis syndrome in patients with metastasis	Post-treatment mortality and histological subtype	Presence of testicular dysgenesis syndrome in deceased patients
IA	11	4	5	-	-	-	0 (% 0)	0	0 (% 0)	1 (NS)	0 (%0)	1 (NS)	0 (%0)
IB	8	4	1	2	-	2	3 (% 23)	2 (NS)	1 (% 50)	1 (M),1(S)	2 (%100)	1 (M),1(S)	2 (%100)
IS	1	1	2	-	-	-	0 (% 0)	1 (M)	0 (% 0)	0		0	
IIA	0	1	0	-	-	-	0 (% 0)	0	0 (% 0)	0		0	
IIB	0	3	1	1	-	1	1 (% 25)	1 (NS)	0 (% 0)	1 (NS)	1 (%100)	1 (NS)	1(%100)
IIC	3	0	0	1	1	-	1 (% 33.3)	1 (S)	1 (% 100)	2 (S)	1 (%50)	2 (S)	1(%50)
IIIA	1	2	0	-	-	1	1 (% 33.3)	1 (NS)	0 (% 0)	1 (NS)	1 (%100)	0	
IIIB	5	3	1	2		2	4 (% 44.4)	2 (NS), 1 (S)	2 (% 66.6)	2(S), 2(NS)	4 (%100)	2(S), 2(NS)	4(%100)
IIIC	6	6	0	3	2	3	6 (% 50)	2 (S), 3 (NS)	4 (% 80)	3(NS), 3(S)	6 (%100)	3(NS), 3(S)	6(%100)
Total number	**35**	**24**	**10**	**9**	**3**	**9**	**16 (% 23.1)**	**14**	**8 (% 57.1)**	**17**	**15 (%88.2)**	**16**	**14(%87.5)**

S = Seminoma, **NS** = Non-seminoma; **M** = Mix germ cell tumor

Table 2 - Demographic, pathological, clinical data and oncologic outcomes of the patients.

Parameters	Group I (Early stage TGCT) (n:33)	Group II (Advanced stage TGCT) (n:36)	Total (n:69)	p value
Age				
Median (25th-75thpercentiles)	31.00 (27.00-37.00)	30.00 (24.25-41.75)	31 (25-40)	† 0.709
Tumor size (cm)				
Median (25th-75thpercentiles)	3.50 (2.15-4.55)	5.55 (3.52-7.20)	4.20 (2.65-6.50)	† 0.002*
Tumor laterality (n,%)				
Left	10 (30.3)	13 (36.1)	23 (33.3)	‡ 0.877
Right	21 (63.6)	21 (58.3)	42 (60.9)	
Bilateral	2 (6.1)	2 (5.6)	4 (5.8)	
Histopathological subtype(n,%)				
Seminoma	19 (57.6)	16 (44.4)	35 (50.7)	
Non-seminoma	8 (24.2)	16 (44.4)	24 (34.8)	‡ 0.202
Mix	6 (18.2)	4 (11.1)	10 (14.5)	
AFP (ng/mL)				
Median (25th-75thpercentiles)	5.00 (1.70-10.70)	6.90 (2.75-354.25)	5.50 (2.15-74.37)	† 0.058
β-hCG (mIU/mL)				
median (25th-75thpercentiles)	4.90 (1.30-33.30)	62.10 (5.95-911.02)	15.20 (2.50-128.00)	† 0.005*
LDH (U/l)				
Median (25th-75thpercentiles)	208.00 (155.00-266.00)	717.00 (330.00-1299.25)	309.00 (202.00-740.00)	†<0.001*
ITGCN (n,%)				
Present	15 (45.5)	20 (55.6)	35 (50.7)	‡ 0.402
Absent	18 (54.5)	16 (44.4)	34 (49.3)	
***Rete testis* involvement (n,%)**				
Present	8 (24.2)	7 (19.4)	15 (21.7)	‡ 0.629
Absent	25 (75.8)	29 (80.6)	54 (78.3)	
Tumor diameter> 4 cm (n,%)				

Yes	12 (36.4)	24 (66.7)	36 (52.2)	‡ 0.012*
No	21 (63.6)	12 (33.3)	33 (47.8)	
Lymphovascular invasion (n,%)				
Present	7 (21.2)	20 (55.6)	27 (39.1)	‡ 0.004*
Absent	26 (78.8)	16 (44.4)	42 (60.9)	
Embryonal carcinoma rate >50% (n,%)				
Present	7 (21.2)	12 (33.3)	19 (27.5)	‡ 0.260
Absent	26 (78.8)	24 (66.7)	50 (72.5)	
Proliferation rate > 70% (n,%)				
Present	3 (9.1)	7 (19.4)	10 (14.5)	‡ 0.222
Absent	30 (90.9)	29 (80.6)	59 (85.5)	
Undescended testis (n,%)				
Present	2 (6.1)	7 (19.4)	9 (13.0)	‡ 0.099
Absent	31 (93.9)	29 (80.6)	60 (87.0)	
Disorders of semen parameters(n,%)				
Present	2 (6.1)	7 (19.4)	9 (13.0)	‡ 0.099
Absent	31 (93.9)	29 (80.6)	60 (87.0)	
Hypospadias (n,%)				
Present	0 (0.0)	3 (8.3)	3 (4.3)	§ 0.240
Absent	33 (100.0)	33 (91.7)	66 (95.7)	
Atrophic testis (n,%)				
Present	1 (3.0)	6 (16.7)	7 (10.1)	‡ 0.061
Absent	32 (97.0)	30 (83.3)	62 (89.9)	
Presence of TDS (n,%)				
Present	3 (9.1)	13 (36.1)	16 (23.2)	‡ 0.008*
Absent	30 (90.9)	23 (63.9)	53 (76.8)	
Local recurrence rate (n,%)	2 (6.1)	12 (33.3)	14 (20.3)	‡ 0.015*
Distant metastasis rate (n,%)	3 (9.1)	14 (38.9)	17 (24.6)	‡ 0.004*
Cancer-specific survival rate (%)	90.9	63.9	76.8	‡ 0.008*

***** = p <0.05 Asteriks (*) indicates statistical significance; **AFP**: alpha-fetoprotein; **β-hCG** = beta human chorionic gonadotropin; **ITGCN** = Intratubular germ cell neoplasia; **LDH** = lactate dehydrogenase; **TDS** = Testicular dysgenesis syndrome; **TGCT** = testicular germ cell tumor
† = Mann-Whitney U test
‡ = Chi-square test
§ = Fisher's Exact test

Figure 1A - KKaplan-Meier plots of recurrence-free survival according to the early and advanced stages for all tumors.

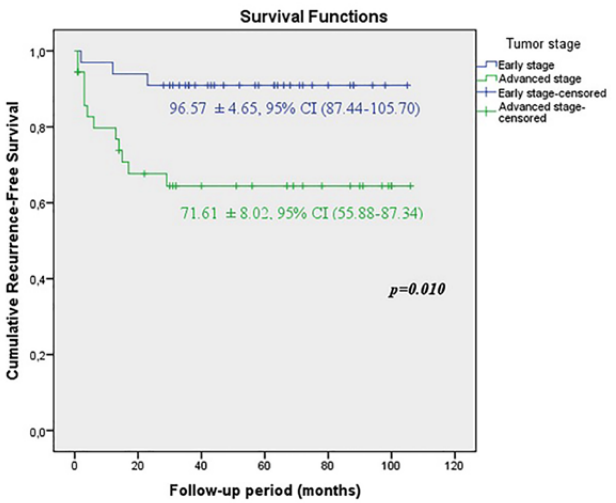
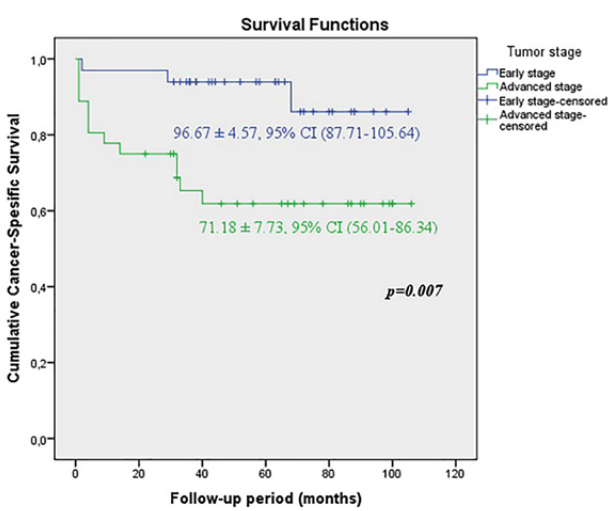


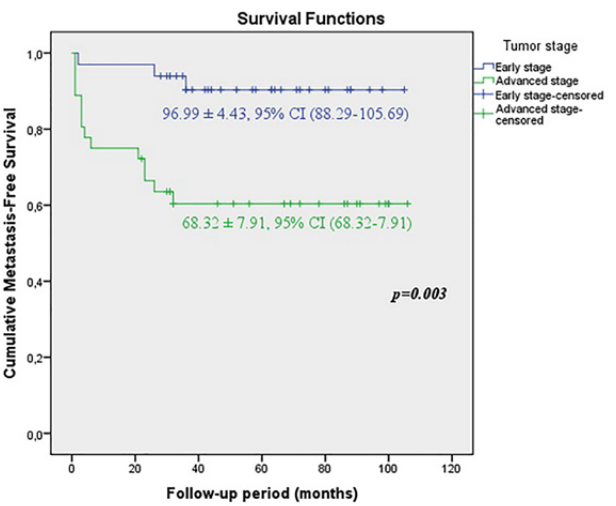
Figure 1B - Kaplan-Meier plots of cancer-specific survival according to the early and advanced stages for all tumors.



(9.14±4.40 vs. 16.22±6.59 months, p <0.001) and CSS (11.71±5.16 vs. 24.11±8.39 months, p <0.001) were statistically shorter in patients with seminoma (Figures 3A, 3B, 3C and Figures 4A, 4B, 4C).

When we evaluated the patients in early and advanced tumor stages, we found that there were no significant differences between the rates of undescended testis, hypospadias and disorders of semen parameters. However, the rate of TDS was found significantly higher

Figure 1C - Kaplan-Meier plots of metastasis-free survival according to the early and advanced stages for all tumors.



in advanced stage (Table-2).

In univariate analysis, clinical stage, β-hCG, LDH, the presences of undescended testis, disorders of semen parameters, hypospadias, atrophic testis and TDS were found as independent predictive factors to estimate local recurrence, distant metastasis and cancer-specific survival (CSS). In multivariate analysis, the most important independent predictive factor was TDS to determine local recurrence, distant metastasis and cancer-specific survival RFS, MFS and CSS in both seminomas and nonseminomas as well as all patients with TGCT. In addition, clinical stage was found as a predictive factor for development of distant metastasis in all patients with TGCT (Table-4).

DISCUSSION

Recent studies in the United States have remarked that TGCT is the most common cancer among men between the ages of 15-44 years and constitutes 98% of all testis malignancies (10). Undescended testis and hypospadias, which are the other components of TDS, affect 2-9% and 0.2-1% of male newborns, respectively (11). Approximately 10-15% of married couples have infertility and the male factor is responsible for about half of the cases

Table 3 - Oncologic outcomes of the patients in terms of testicular dysgenesis syndrome.

All patients with testicular germ cell tumor	Patients with TDS (n:16)	Patients without TDS (n:53)	Total (n:69)	p value
Local recurrence(n,%)				
Present	12 (75.0)	3 (5.7)	16 (23.2)	‡<0.001*
Absent	4 (25.0)	50 (94.3)	53 (76.8)	
Distant metastasis (n,%)				
Present	15 (93.6)	2 (3.8)	17 (24.6)	‡<0.001*
Absent	1 (6.3)	51 (96.2)	52 (75.4)	
Cancer spesific mortality (n,%)				
Present	14 (87.5)	2 (3.8)	16 (23.2)	‡<0.001*
Absent	2 (12.5)	51 (96.2)	53 (76.8)	
Patients with seminoma	**Patients with TDS (n:7)**	**Patients without TDS (n:28)**	**Total (n:35)**	**p value**
Local recurrence(n,%)				
Present	4 (57.1)	1 (3.6)	5 (14.3)	§ 0.003*
Absent	3 (42.9)	27 (96.4)	30 (85.7)	
Distant metastasis (n,%)				
Present	7 (100.0)	1 (3.6)	8 (22.9)	§ <0.001*
Absent	0 (0.0)	27 (96.4)	27 (77.1)	
Cancer specific mortality (n,%)				
Present	7 (100.0)	1 (3.6)	8 (22.9)	§ <0.001*
Absent	0 (0.0)	27 (96.4)	27 (77.1)	
Patients with non-seminoma	Patients with TDS (n:9)	Patients without TDS (n:25)	Total (n:34)	p value
Local recurrence(n,%)				
Present	8 (88.9)	1 (4.0)	9 (26.5)	§ <0.001*
Absent	1 (11.1)	24 (96.0)	25 (73.5)	
Distant metastasis (n,%)				
Present	8 (88.9)	1 (4.0)	9 (26.5)	§ <0.001*
Absent	1 (11.1)	24 (96.0)	25 (73.5)	
Cancer specific mortality (n,%)				
Present	7 (77.8)	1 (4.0)	8 (23.5)	§ <0.001*
Absent	2 (22.2)	24 (96.0)	26 (76.5)	

***** = p <0.05 Asteriks (*) indicates statistical significance.
TDS = Testicular dysgenesis syndrome
‡ = Chi-square test
§ = Fisher's Exact test

Figure 2A - Kaplan-Meier plots of recurrence-free survival according to presence of Testicular Dysgenesis Syndrome for all patients.

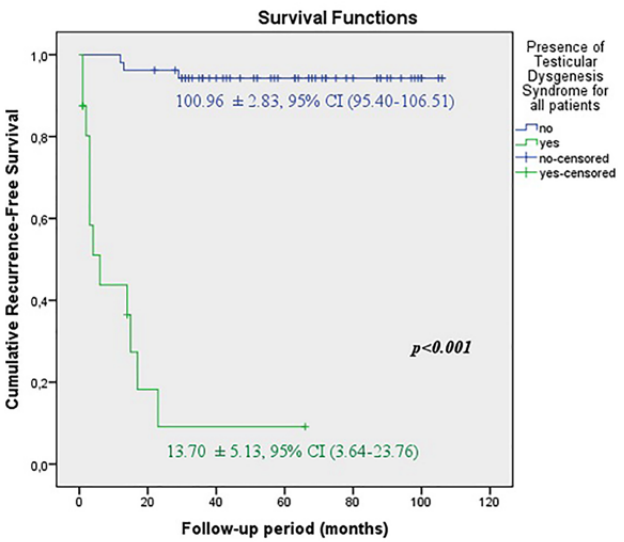
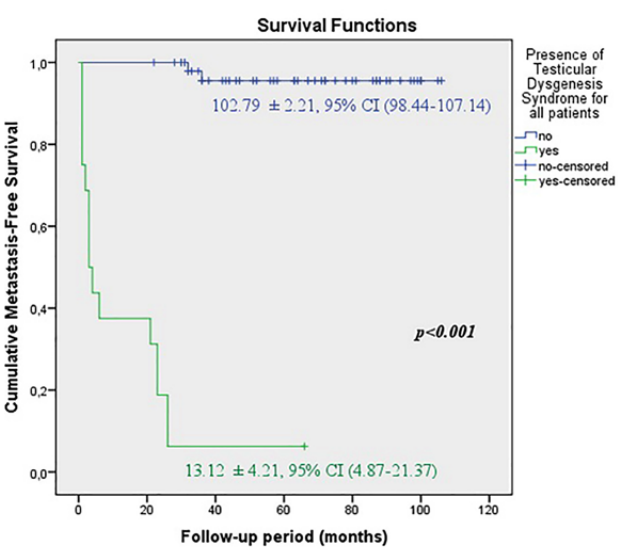


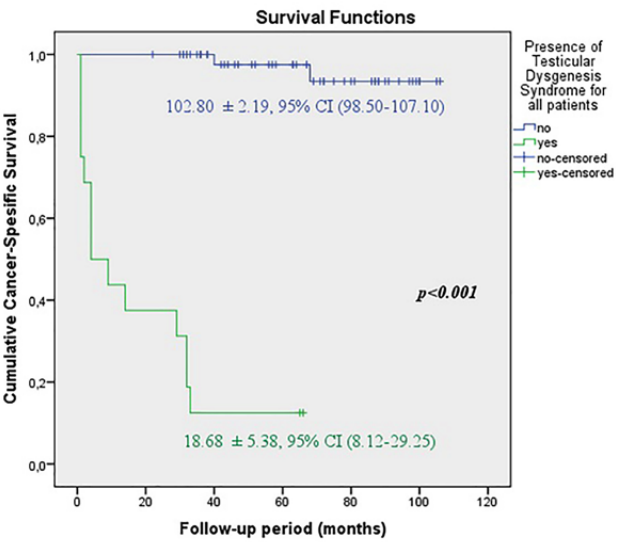
Figure 2B - Kaplan-Meier plots of metastasis-free survival according to presence of Testicular Dysgenesis Syndrome for all patients.



(12). Although most of these disorders are assumed to be associated with TDS, further studies are needed to make the definition of TDS widely acceptable (13).

It is thought that embryonic hormonal disturbances related to androgens play a role on abnormal differentiation of primordial germ cells (14). These are usually manifested by antenatal origin. Undescended testis and hypospadias give

Figure 2C - Kaplan-Meier plots of cancer-specific survival according to presence of Testicular Dysgenesis Syndrome for all patients.



symptoms at neonatal period whereas poor quality of semen and development of TGCT manifest after puberty (9). Animal models and epidemiological researches have revealed that deficiencies in the production of androgens, disorders of androgen receptor expression, disturbance in androgen levels, exposure to anti-androgenic or estrogenic disruptors were attributed to the pathogenesis of TDS (6, 15). These factors are blamed for causing dysfunctions and dysregulation of Leydig and Sertoli cells. As a result, disruption of testicular differentiation and development give rise to impairment of normal gonadal maturation. Consequently, irreversible testicular dysgenesis is unavoidable and it results in genital malformation (such as hypospadias and undescended testis), impaired spermatogenesis and TGCT (7). TDS is predominantly triggered by environmental exposure, genetic and lifestyle factors as well as embryonic hormonal disturbances. All of these predisposing factors similarly affect the pathophysiology of TDS.

Skakkebaek et al. (16) re-analysed 20 testicular biopsies which were derived from patients with infertility, undescended testis and hypospadias. TGCT was detected in 45% of patients. But they did not evaluate the relation between presence of TDS and TGCT prognosis. Guminska et al. (17) detected that testes with disturbed spermatogenesis

Figure 3A - Kaplan-Meier plots of recurrence-free survival according to presence of Testicular Dysgenesis Syndrome for patients with seminoma.

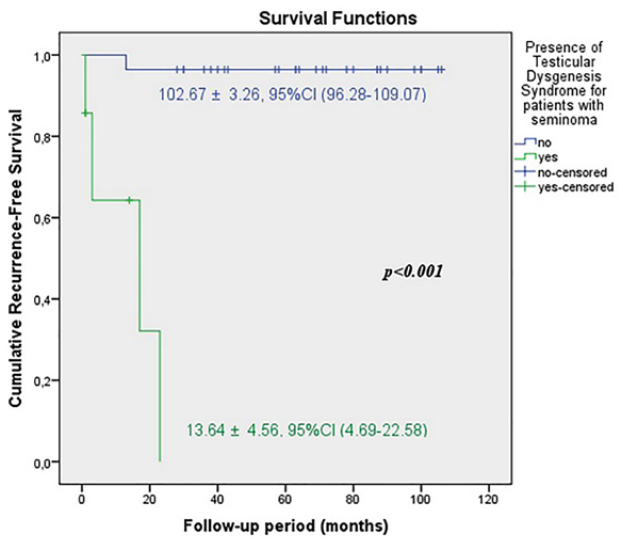
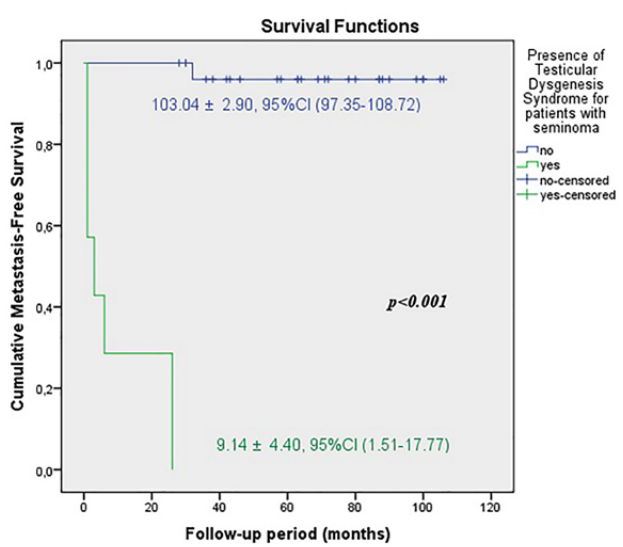
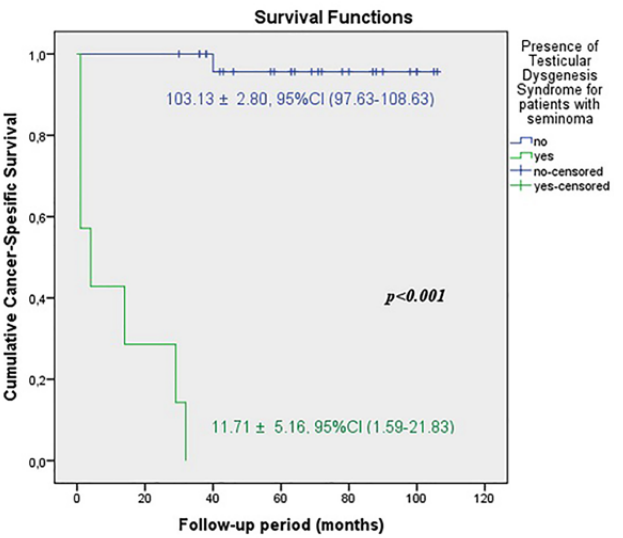


Figure 3B - Kaplan-Meier plots of metastasis-free survival according to presence of Testicular Dysgenesis Syndrome for patients with seminoma.



were more prone to development of TGCT. They investigated morphometric analysis of seminiferous epithelium, qualitative and quantitative features of Leydig cells, seminiferous tubules diameter and thickness of tubular wall. It was shown that poor testicular histomorphological features related to testicular dysgenesis increased the incidence of

Figure 3C - Kaplan-Meier plots of cancer-specific survival according to presence of Testicular Dysgenesis Syndrome for patients with seminoma.



TGCT but they did not worsen the tumor prognosis.

Another source that supports the biological mechanism of TDS, can be attributed to our knowledge about testicular microlithiasis (TM). TM which is detected incidentally during the scrotal ultrasound, is a rare condition. It is observed around 0.6-9.0% in symptomatic male adults and around 2.4-5.6% in asymptomatic males (17). Although the presence of TM alone is not an indication for further investigation, the presence of other risk factors carries risk for TGCT development. These risk factors include history of previous TGCT, undescended testis, orchidopexy, testicular atrophy (testicular volume <12mL) and subfertility (18). As it can be understood, the risk of TGCT increases in the presence of undescended testis and subfertility (19). From this point of view, we can think that embryological development and pathogenesis of all these disorders mentioned above is caused by a common fetal origin. This condition can be interpreted as supporting the TDS hypothesis (20).

It should be known that TDS hypothesis does not mean that all affected men develop all four components (21). A very broad variety of phenotypes can be seen in TDS. This wide spectrum ranges from genetically determined "Disorders of Sex Development" to mild forms such as slightly

Figure 4A - Kaplan-Meier plots of recurrence-free survival according to presence of Testicular Dysgenesis Syndrome for patients with non-seminoma.

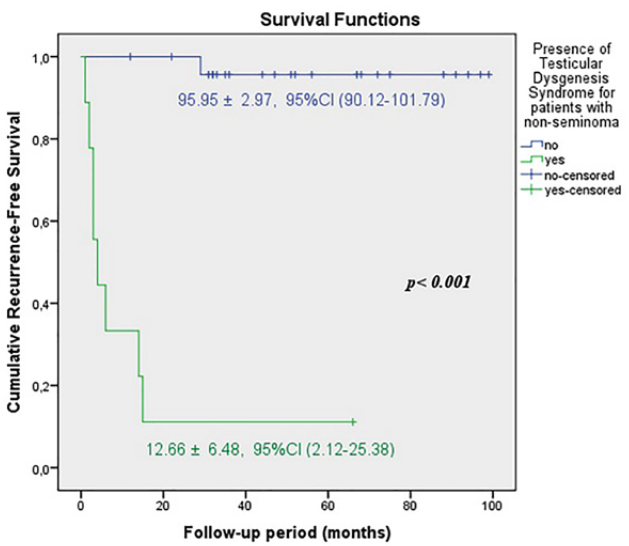
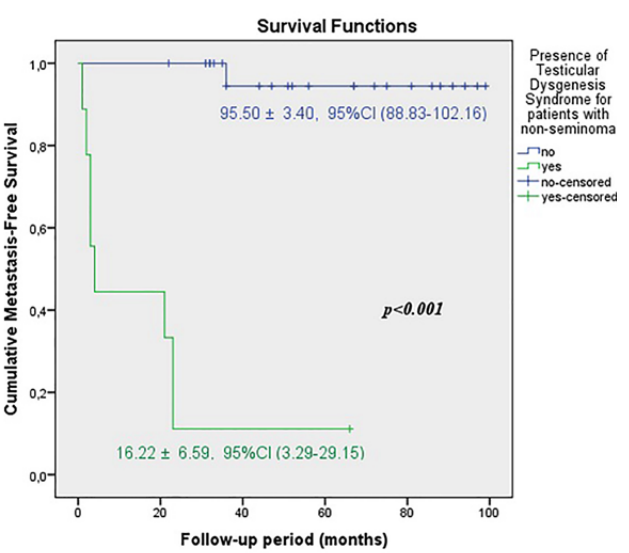
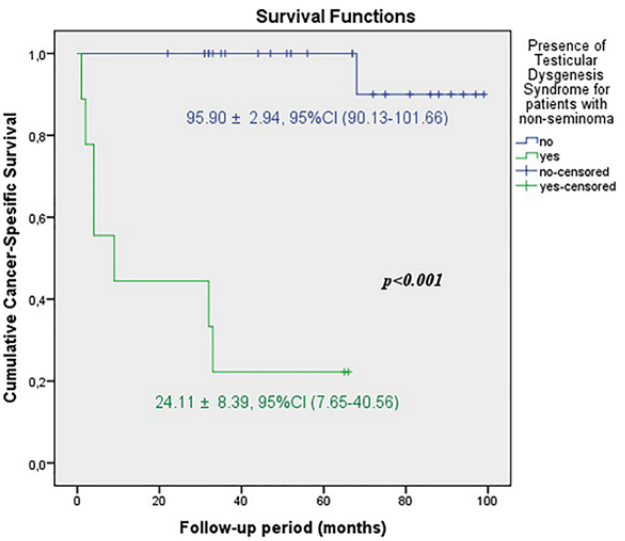


Figure 4B - Kaplan-Meier plots of metastasis-free survival according to presence of Testicular Dysgenesis Syndrome for patients with non-seminoma.



decreased spermatogenesis (5). One component of TDS may increase the possibility of other components' existence. Especially, if there are more than one component, the presence of other components should be examined more carefully to detect TDS (22).

Figure 4C - Kaplan-Meier plots of cancer-specific survival according to presence of Testicular Dysgenesis Syndrome for patients with non-seminoma.



Environmental factors and genetic susceptibility are responsible for the etiology of TDS and TGCT (15). In literature, there are many animal models and epidemiological studies demonstrating this relationship (13, 15). Current animal models, involving fetal exposure to "Di-n-butyl phthalate" have been highlighting that environmental factors are most likely responsible for TDS and TGCT (4, 5). Translation of the animal model's findings to the human biology have been linked to TDS (4). But we have found no detailed studies investigating whether TDS or its components affect the oncological outcomes of TGCT.

Cure is achievable in 95% of all patients with TGCT. At the time of diagnosis, 75-80% of seminomas are stage I. In this group, rete testis invasion and/or tumor size larger than 4 cm are risk factors that predict relapse and occult metastasis. In the follow-up periods of seminomas after adjuvant therapy, systemic recurrence rate was 1-4%, while occult metastasis rate was 10-15%. If any adjuvant treatments are not given to the patients with risk factors, the rate of local recurrence or retroperitoneal metastasis in five years is 15-20% (23). 55% of non-seminomas are stage I at the time of diagnosis. The worst risk factor that predict relapse and occult metastasis is LVI for non-seminomas, while other important prognostic

risk factors are percentage of embryonal carcinoma >50% and a proliferation rate >70%. More than 30% of them have occult metastasis at diagnosis. 70% of them can develop local recurrence if any adjuvant treatments are not performed to the patients with risk factors. In the presence of LVI, systemic relapse rate was 14-22% and occult metastasis rate was 48% (24).

The local recurrence rates were reported as 9-24% in stage IIA/B, whereas the cure rate is approximately 80% in stage IIC/III, despite the frontline and salvage chemotherapy (25). In metastatic disease, 5-year survival rates were reported by the International Germ Cell Cancer Collaboration Group to be 91% in the favorable risk group, 79% in the intermediate risk group and 48% in the poor risk group (25).

In our study, during median 57 (6-106) months follow-up in all patients, local recurrence rate was 21.7%, distant metastasis rate was 24.6%, 5-year cancer specific survival CSS rate was 76.8%. When our patients were divided into two groups as early and advanced stages, the rates of local recurrence, distant metastasis and 5-year cancer specific survival were 9.1%, 9.1%, 90.9% for early stage respectively, whereas the rates were 33.3%, 38.9% and 63.9% for advanced stage. The duration of recurrence-free survival RFS (96.57 ± 4.65 months), metastasis-free survival MFS (96.99 ± 4.43 months), cancer-specific survival CSS (96.67 ± 4.57 months) were observed significantly higher in early stage. Although our survival rates are less than the rates in the current literature (26), this may be explained by the small patients populations and short follow-up periods.

Undescended testis is known to be an important risk factor for the development of TGCT. The relative risk of TGCT was 2.23 even if patients underwent orchiopexy before 13 years old (27). Moirano et al. (28) observed that undescended testis was higher in TGCT group (11.4%) than in healthy control group (3.0%). Hanson et al. (29) detected an increased risk of testicular cancer (hazard rate of 3.3) in subfertile men when compared with fertile men (29). In addition, hypospadias was found associated with an increased relative risk for TGCT development (hazard rate of 2.13) (30).

We could not evaluate whether undescended testis, disorders of semen parameters and hypospadias were risk factors for the development of TGCT because we did not have a healthy control group. We compared these three components in terms of tumor stages. When these components were analyzed individually, we did not find significantly differences between early and advanced stage groups. But the rate of TDS was significantly higher in patients with advanced stage. This finding suggested that even if the components alone did not contain poor prognostic features for TGCT development, a significant increase was observed in tumor stages in the patients diagnosed with TDS (having more than one component).

In subgroup analysis, we divided patients into two groups according to presence of TDS. Although the small numbers of patients in the TDS group decreased the statistical power of the study, we found significantly higher rates of local recurrence (75% vs. 5.7), distant metastasis (93.6% vs 3.8%) and cancer related mortality (87.5% vs. 3.8%) in TDS group rather than those without TDS. When we evaluated two different tumor types separately, in the presence of TDS, the rate of local recurrence (88.9% vs. 57.1%) was higher in non-seminomas; whereas distant metastasis (100% vs. 88.9%) and cancer-specific mortality rates (100% vs. 77.8%) were higher in seminomas. It is obvious that these findings will be more reliable when a much larger patient population is evaluated.

To the best of our knowledge, this is the first study to evaluate the prognostic value of TDS components on TGCT prognosis and oncological outcomes. However, this study has some limitations. The main limitations of our study are retrospective, non randomized design with small patient population in a single center. Future studies that have larger numbers of patients with multicentre, prospective, randomized, controlled, long-term follow-up are needed to verify our results and explain more new details about this hypothesis, especially for the subgroup analysis with patients having TDS. We presented our findings as "Preliminary Results" because it was not easy to have comprehensive results due to small patient population and relatively short follow-up. Since this topic has not been studied before, we think that our findings as "Preliminary Results" may be a step for further studies.

Table 4 - Predictive factors for local recurrence, distant metastases and cancer-specific survival.

All patients with testicular germ cell tumor	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		**p**
Development of local recurrence		Lower	Upper			Lower	Upper	
Clinical stage	12,471	2,320	34,624	**0.005**				
β-hCG	1,001	1,000	1,011	**0.003**				
LDH	1,009	1,000	1,019	**<0.001**				
Undescended testis	20,238	9,128	106,902	**<0.001**				
Disorders of semen parameters	7,250	2,359	22,281	**0.001**				
Hypospadiass	16,182	4,286	61,100	**<0.001**				
Atrophic testis	11,186	3,641	34,373	**<0.001**				
Testicular Dysgenesis Syndrome	31,911	12,414	289,130	**<0.001**	31,911	12,414	289,130	**<0.001**

All patients with testicular germ cell tumor	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		p
Development of distant metastasis		Lower	Upper			Lower	Upper	
Clinical stage	14,988	5,575	36,668	**0.001**	12,827	4,186	36,738	**0.019**
β-hCG	1,003	1,000	1,008	**0.007**				
LDH	1,004	1,000	1,017	**0.001**				
Undescended testis	11,966	5,069	44,184	**<0.001**				
Disorders of semen parameters	12,928	5,316	41,917	**<0.001**				
Hypospadiass	11,342	3,082	41,741	**<0.001**				
Atrophic testis	11,626	4,009	33,711	**<0.001**				
Testicular Dysgenesis Syndrome	35,120	15,785	357,499	**<0.001**	35,120	15,785	357,499	**<0.001**

All patients with testicular germ cell tumor	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		p
Cancer spesific survival		Lower	Upper			Lower	Upper	
Clinical stage	12,404	2,339	33,316	**0.003**				
β-hCG	1,002	1,000	1,016	**0.006**				
LDH	1,006	1,000	1,014	**0.001**				

Undescended testis	19,559	6,302	60,709	**<0.001**				
Disorders of semen parameters	10,602	3,729	30,143	**<0.001**				
Hypospadiass	12,398	3,317	46,342	**<0.001**				
Atrophic testis	11,661	4,000	33,994	**<0.001**				
Testicular Dysgenesis Syndrome	37,148	12,844	780,852	**<0.001**	37,148	12,844	780,852	**<0.001**

Patients with seminoma	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		p
Development of local recurrence		Lower	Upper			Lower	Upper	
Clinical stage	12,564	0,926	7,101	**0.047**				
LDH	1,001	1,000	1,002	**0.038**				
Undescended testis	13,159	3,790	141,529	**0.001**				
Disorders of semen parameters	9,347	1,449	60,312	**0.019**				
Hypospadiass	15,641	3,555	184,944	**0.001**				
Atrophic testis	18,323	2,931	114,540	**0.002**				
Testicular Dysgenesis Syndrome	30,628	4,635	129,742	**0.001**	30,628	4,635	129,742	**0.001**

Patients with seminoma	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		p
Development of distant metastasis		Lower	Upper			Lower	Upper	
Clinical stage	12,766	1,179	6,493	**0.019**				
β-hCG	1,005	1,001	1,010	**0.020**				
LDH	1,002	1,000	1,009	**0.016**				
Undescended testis	9,470	2,111	42,487	**0.003**				
Disorders of semen parameters	11,228	5,605	43,994	**<0.001**				
Hypospadiass	9,076	1,735	47,469	**0.009**				
Atrophic testis	13,015	2,880	58,805	**0.001**				
Testicular Dysgenesis Syndrome	44,261	5,898	411,469	**<0.001**	44,261	5,898	411,469	**<0.001**

Patients with seminoma	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		p
Cancer specific survival		Lower	Upper			Lower	Upper	
Clinical stage	12,766	1,177	6,502	**0.020**				
β-hCG	1,000	0,997	1,007	**0.020**				
LDH	1,001	0,987	1,024	**0.018**				
Undescended testis	10,323	2,274	46,861	**0.002**				
Disorders of semen parameters	9,891	6,011	21,240	**<0.001**				
Hypospadiass	8,991	1,720	46,989	**0.009**				
Atrophic testis	14,310	3,097	66,129	**0.001**				
Testicular Dysgenesis Syndrome	49,691	2,004	338,743	**0.026**	49,691	2,004	338,743	**0.026**

Patients with non-seminoma	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		p
Development of local recurrence		Lower	Upper			Lower	Upper	
Clinical stage	12,317	1,041	5,157	**0.039**				
LDH	1,000	0,879	1,011	**0.005**				
Undescended testis	18,411	6,143	81,928	**<0.001**				
Disorders of semen parameters	5,827	1,439	23,594	**0.014**				
Hypospadiass	2,457	1,203	4,916	**0.045**				
Atrophic testis	8,680	1,906	39,534	**0.005**				
Testicular Dysgenesis Syndrome	42,666	6,542	173,660	**<0.001**	42,666	6,542	173,660	**<0.001**

Patients with non-seminoma	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		p
Development of distant metastasis		Lower	Upper			Lower	Upper	
Clinical stage	12,342	1,057	5,190	**0.036**				
β-hCG	1,005	1,001	1,010	**0.020**				
LDH	1,000	0,984	1,003	**0.005**				
Undescended testis	14,095	4,720	122,992	**<0.001**				
Disorders of semen parameters	6,603	1,610	27,083	**0.009**				

Hypospadiass	2,123	1,015	3,356	**0.042**				
Atrophic testis	6,456	1,538	27,102	**0.011**				
Testicular Dysgenesis Syndrome	28,536	9,458	39,177	**0.046**	28,536	9,458	39,177	**0.046**

Patients with non-seminoma	Univariate Model				Multivariate Model			
	HR	%95 Confidence Interval		p	HR	%95 Confidence Interval		p
Cancer specific survival		Lower	Upper			Lower	Upper	
Clinical stage	12,238	0,969	5,168	**0.039**				
β-hCG	1,000	0,997	1,007	**0.020**				
LDH	1,002	0,802	1,011	**0.005**				
Undescended testis	15,891	5,827	44,495	**<0.001**				
Disorders of semen parameters	4,095	0,790	21,219	**0.033**				
Hypospadiass	1,402	1,017	3,916	**0.041**				
Atrophic testis	8,372	1,849	37,908	**0.006**				
Testicular Dysgenesis Syndrome	25,634	2,479	39,951	**0.034**	25,634	2,479	39,951	**0.034**

p <0.05 Bold values indicates statistical significance.
β-hCG = beta human chorionic gonadotropin; **HR** = hazard ratio; **LDH** = lactate dehydrogenase
Cox Regression Analysis

CONCLUSIONS

In conclusion, although there have been many controversial views on TDS since the last two decades, most studies have shown the relationship between the four components of TDS. We observed the fact that TDS was detected to be higher in advanced stages of TGCT. Moreover, we have seen a significant increase in the rates of local recurrence, distant metastasis and cancer specific mortality in the presence of TDS.

ABBREVIATIONS

AFP = Alpha-fetoprotein;
β-hCG = Beta human chorionic gonadotropin;
LDH = Lactate dehydrogenase;
LVI = lymphovascular invasion;
TDS = Testicular Dysgenesis Syndrome;
TGCT = Testicular germ cell tumor;
TM = Testicular microlithiasis.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod. 2001;16:972-8.
2. Jørgensen N, Asklund C, Carlsen E, Skakkebaek NE. Coordinated European investigations of semen quality: results from studies of Scandinavian young men is a matter of concern. Int J Androl. 2006;29:54-61; discussion 105-8.
3. Sharpe RM, Skakkebaek NE. Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. Fertil Steril. 2008;89(2 Suppl):e33-8.
4. van den Driesche S, Kilcoyne KR, Wagner I, Rebourcet D, Boyle A, Mitchell R, et al. Experimentally induced testicular dysgenesis syndrome originates in the masculinization programming window. JCI Insight. 2017;2:e91204.

5. Jørgensen N, Rajpert-De Meyts E, Main KM, Skakkebaek NE. Testicular dysgenesis syndrome comprises some but not all cases of hypospadias and impaired spermatogenesis. Int J Androl. 2010;33:298-303.
6. van den Driesche S, Kolovos P, Platts S, Drake AJ, Sharpe RM. Inter-relationship between testicular dysgenesis and Leydig cell function in the masculinization programming window in the rat. PLoS One. 2012;7:e30111.
7. Söder O. Sexual dimorphism of gonadal development. Best Pract Res Clin Endocrinol Metab. 2007;21:381-91.
8. Akre O, Richiardi L. Does a testicular dysgenesis syndrome exist? Hum Reprod. 2009;24:2053-60.
9. Spiller CM, Bowles J. Germ cell neoplasia in situ: The precursor cell for invasive germ cell tumors of the testis. Int J Biochem Cell Biol. 2017;86:22-25.
10. McGlynn KA, Cook MB. Etiologic factors in testicular germ-cell tumors. Future Oncol. 2009;5:1389-402.
11. Toppari J, Virtanen HE, Main KM, Skakkebaek NE. Cryptorchidism and hypospadias as a sign of testicular dysgenesis syndrome (TDS): environmental connection. Birth Defects Res A Clin Mol Teratol. 2010;88:910-9.
12. Erdemir F, Fırat F, Gençten Y. The Evaluation and Clinical Significance of Sperm Morphology. Turk Urol Sem. 2011;2:11-7.
13. Rajpert-De Meyts E. Developmental model for the pathogenesis of testicular carcinoma in situ: genetic and environmental aspects. Hum Reprod Update. 2006;12:303-23.
14. Baskin LS. Hypospadias and urethral development. J Urol. 2000;163:951-6.
15. Xing JS, Bai ZM. Is testicular dysgenesis syndrome a genetic, endocrine, or environmental disease, or an unexplained reproductive disorder? Life Sci. 2018;194:120-129.
16. Skakkebaek NE, Holm M, Hoei-Hansen C, Jørgensen N, Rajpert-De Meyts E. Association between testicular dysgenesis syndrome (TDS) and testicular neoplasia: evidence from 20 adult patients with signs of maldevelopment of the testis. APMIS. 2003;111:1-9; discussion 9-11.
17. Guminska A, Oszukowska E, Kuzanski W, Sosnowski M, Wolski JK, Walczak-Jedrzejowska R, et al. Less advanced testicular dysgenesis is associated by a higher prevalence of germ cell neoplasia. Int J Androl. 2010;33:e153-62.
18. Balawender K, Orkisz S, Wisz P. Testicular microlithiasis: what urologists should know. A review of the current literature. Cent European J Urol. 2018;71:310-314.
19. Pedersen MR, Rafaelsen SR, Møller H, Vedsted P, Osther PJ. Testicular microlithiasis and testicular cancer: review of the literature. Int Urol Nephrol. 2016;48:1079-86.
20. Dantsev IS, Ivkin EV, Tryakin AA, Godlevski DN, Latyshev OY, Rudenko VV, et5 al. Genes associated with testicular germ cell tumors and testicular dysgenesis in patients with testicular microlithiasis. Asian J Androl. 2018;20:593-599.
21. Mahood IK, Hallmark N, McKinnell C, Walker M, Fisher JS, Sharpe RM. Abnormal Leydig Cell aggregation in the fetal testis of rats exposed to di (n-butyl) phthalate and its possible role in testicular dysgenesis. Endocrinology. 2005;146:613-23.
22. Hoei-Hansen CE, Sommer P, Rajpert-De Meyts E, Skakkebaek NE. A rare diagnosis: testicular dysgenesis with carcinoma in situ detected in a patient with ultrasonic microlithiasis. Asian J Androl. 2005;7:445-7.
23. Shelley MD, Burgon K, Mason MD. Treatment of testicular germ-cell cancer: a cochrane evidence-based systematic review. Cancer Treat Rev. 2002;28:237-53.
24. Ondrusova M, Suchansky M, Psota M, Zeleny T, Ondrus D. Late relapse in stage I of nonseminomatous germ cell testicular cancer on surveillance. Bratisl Lek Listy. 2018;119:3-5.
25. Adra N, Einhorn LH. Testicular cancer update. Clin Adv Hematol Oncol. 2017;15:386-396.
26. Withington J, Cole AP, Meyer CP, Seisen T, Schmid M, Lipsitz SR, et al. Comparison of testis cancer-specific survival: an analysis of national cancer registry data from the USA, UK and Germany. BJU Int. 2019;123:385-387.
27. Pettersson A, Richiardi L, Nordenskjold A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med. 2007;356:1835-41.
28. Moirano G, Zugna D, Grasso C, Mirabelli D, Lista P, Ciuffreda L, et al. Postnatal risk factors for testicular cancer: The EPSAM case-control study. Int J Cancer. 2017;141:1803-1810.
29. Hanson HA, Anderson RE, Aston KI, Carrell DT, Smith KR, Hotaling JM. Subfertility increases risk of testicular cancer: evidence from population-based semen samples. Fertil Steril. 2016;105:322-8.e1.
30. Schnack TH, Poulsen G, Myrup C, Wohlfahrt J, Melbye M. Familial coaggregation of cryptorchidism, hypospadias, and testicular germ cell cancer: a nationwide cohort study. J Natl Cancer Inst. 2010;102:187-92.

Correspondence address:
Ismail Selvi, MD, FEBU
Department of Urology,
Karabuk University Training and Research Hospital,
Karabuk, 78200, Turkey
Fax: + 90 0370 412-56 28
E-mail: ismselvi33@hotmail.com

EDITORIAL COMMENT

Vol. 46 (5): 741-742, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0387.1

Editorial Comment: Effects of testicular dysgenesis syndrome components on testicular germ cell tumor prognosis and oncological outcomes

Andréia Cristina de Melo [1]

[1] *Divisão de Pesquisa Clínica, Instituto Nacional do Câncer do Brasil – INCA, Rio de Janeiro, RJ, Brasil*

COMMENT

Testicular cancer is the most curable solid tumor and the most common malignancy in men between the ages of 18 and 35 years, although it accounts for just 1% of all cancers in men (1). Testicular germ cell tumors account for 95% of testicular cancers which are classified as either seminomas or non-seminomas (2).

There are a variety of known risk factors for testicular neoplasia, including cryptorchidism (3), history of hypospadias (4), individuals with androgen insensitivity syndrome or mixed gonadal dysgenesis (5, 6), a personal or family history of testicular cancer, infertility or subfertility (7) and HIV infection (8). All of these risk factors predispose to the development of carcinoma in situ and invasive testicular cancer.

Testicular dysgenesis syndrome composed by undescended testis, hypospadias, decreased spermatogenesis and testicular germ cell tumor has also been recently described (9). Thus far, there has been a lack of information regarding the effects of the testicular dysgenesis syndrome on the testicular germ cell tumor prognosis.

The current issue of the International Brazilian Journal of Urology presents an interesting original paper from a Turkish group. Selvi and colleagues on the paper entitled “Effects of testicular dysgenesis syndrome components on testicular germ cell tumor prognosis and oncological outcomes” (10) retrospectively assessed the clinical characteristics and oncological outcomes of 69 patients who underwent radical orchiectomy due to testicular germ cell tumor. In a subgroup analysis, higher testicular dysgenesis syndrome rates were found in advanced stage testicular tumors (36.1% versus 9.1%; p=0.008). The group with testicular dysgenesis syndrome had higher local recurrence, distant metastasis, and also higher cancer-specific mortality in comparison to the group without the syndrome (the differences were statistically significant, p<0.001 for the 3 outcomes). In terms of survival, the recurrence-free survival, the metastasis-free survival and the cancer-specific survival were statistically significant lower in the group of patients with testicular dysgenesis syndrome. In the multivariate analysis, testicular dysgenesis syndrome was the most important independent predictive factor related with local recurrence, distant metastasis, recurrence-free survival, metastasis-free survival and cancer-specific survival in both seminomas and non-seminomas, and also for the entire group of patients diagnosed with testicular germ cell tumor.

Despite the originality of this scientific report, some limitations must be addressed, since it is based on a small retrospective single center cohort, susceptible to selection bias once the patients whose data could not be completed were excluded from the study.

Finally, this is a thought-provoking hypothesis which is generating research. Further studies are warranted in order to confirm the current findings.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
2. Walsh TJ, Grady RW, Porter MP, Lin DW, Weiss NS. Incidence of testicular germ cell cancers in U.S. children: SEER program experience 1973 to 2000. Urology. 2006;68:402-5; discussion 405.
3. Oh J, Landman J, Evers A, Yan Y, Kibel AS. Management of the postpubertal patient with cryptorchidism: an updated analysis. J Urol. 2002;167:1329-33.
4. Schnack TH, Poulsen G, Myrup C, Wohlfahrt J, Melbye M. Familial coaggregation of cryptorchidism, hypospadias, and testicular germ cell cancer: a nationwide cohort study. J Natl Cancer Inst. 2010;102:187-92.
5. Levin HS. Tumors of the testis in intersex syndromes. Urol Clin North Am. 2000;27:543-51, x.
6. Gourlay WA, Johnson HW, Pantzar JT, McGillivray B, Crawford R, Nielsen WR. Gonadal tumors in disorders of sexual differentiation. Urology. 1994;43:537-40.
7. Richiardi L, Akre O, Montgomery SM, Lambe M, Kvist U, Ekbom A. Fecundity and twinning rates as measures of fertility before diagnosis of germ-cell testicular cancer. J Natl Cancer Inst. 200421;96:145-7.
8. Garolla A, Vitagliano A, Muscianisi F, Valente U, Ghezzi M, Andrisani A, et al. Role of Viral Infections in Testicular Cancer Etiology: Evidence From a Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2019;10:355.
9. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod. 2001;16:972-8.
10. Selvi I, Ozturk E, Yikilmaz TN, Sarikaya S, Basar H Jr. Effects of testicular dysgenesis syndrome components on testicular germ cell tumor prognosis and oncological outcomes. Int Braz J Urol. 2020;46:725-40.

ARTICLE INFO

Andreia Cristina de Melo
https://orcid.org/0000-0002-1201-4333

Int Braz J Urol. 2020; 46: 741-2

Submitted for publication:
May 14, 2020

Accepted:
May 22, 2020

Andréia Cristina de Melo, MD, PhD

Divisão de Pesquisa Clínica,
Instituto Nacional do Câncer do Brasil – INCA,
Rio de Janeiro, RJ, Brasil
E-mail: melo.andreia@uol.com.br

ORIGINAL ARTICLE

Vol. 46 (5): 743-751, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0388

Self-perception, quality of life and ease of catheterization in patients with continent urinary diversion with the mitrofanoff principle

Julián Chavarriaga [1], Nicolás Fernández [1,2,3], María A. O. Campo [1], John Bolivar [1], German Patiño [1,4], Jaime Perez [1,2]

[1] Division of Urology, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogotá, Colombia; [2] Division of Urology, Fundación Santa Fe de Bogotá, Colombia; [3] Division of Urology, Hospital for SickKids, University of Toronto, Canada; [4] Division of Urology, University of California San Francisco, United States of America

ABSTRACT

Purpose: Continent urinary diversion (CUD) with the Mitrofanoff principle stands as an alternative to urethral catheterization by a route other than the urethra. The aim of the study was to determine self-perception of health-related quality of life (HRQoL), ease of catheterization and global and cosmetic outcomes in patient's dependent on Mitrofanoff catheterization.

Materials and methods: Records of all patients who underwent CUD with the Mitrofanoff principle between 2012 to 2018 were reviewed. Data were collected and analysed retrospectively from medical charts. We assessed HRQoL with the EuroQol EQ-5D-3L questionnaire, cosmetic and global satisfaction with a questionnaire designed by the reconstructive urology board and ease of catheterization with a Likert questionnaire adapted from the Intermittent Catheterization Difficulty Questionnaire (ICDQ) validated in patients reliant on retrograde CIC.

Results: A total of 25 patients requiring CUD with the Mitrofanoff principle between 2012 and 2018 were assessed, the group was composed mainly of: appendiceal conduits 18 patients (72%) and 7 ileal conduits (Yang-Monti) and three of those requiring Casale (Monti Spiral) and 1 a double Monti technique. Median follow-up was 57 months, median age was 30 years. Visual Analogue Scale (VAS) of the EQ-5D-3L reported a Global health score of 86.5%. Fifty nine percent of the patients had no pain or bleeding with catheterizations. Regarding global satisfaction and cosmetic perception 91% were satisfied with their CUD.

Conclusions: CUD is associated with good HRQoL, global satisfaction, ease and painless catheterization, adequate self-perception of cosmetic outcomes and a low complication rate, remaining a safe and viable option.

ARTICLE INFO

Julián Chavarriaga
http://orcid.org/0000-0003-0158-504X

Keywords:
Urinary Diversion; Quality of Life; Urinary Bladder, Neurogenic

Int Braz J Urol. 2020; 46: 743-51

Submitted for publication:
June 12, 2019

Accepted after revision:
November 06, 2019

Published as Ahead of Print:
April 10, 2020

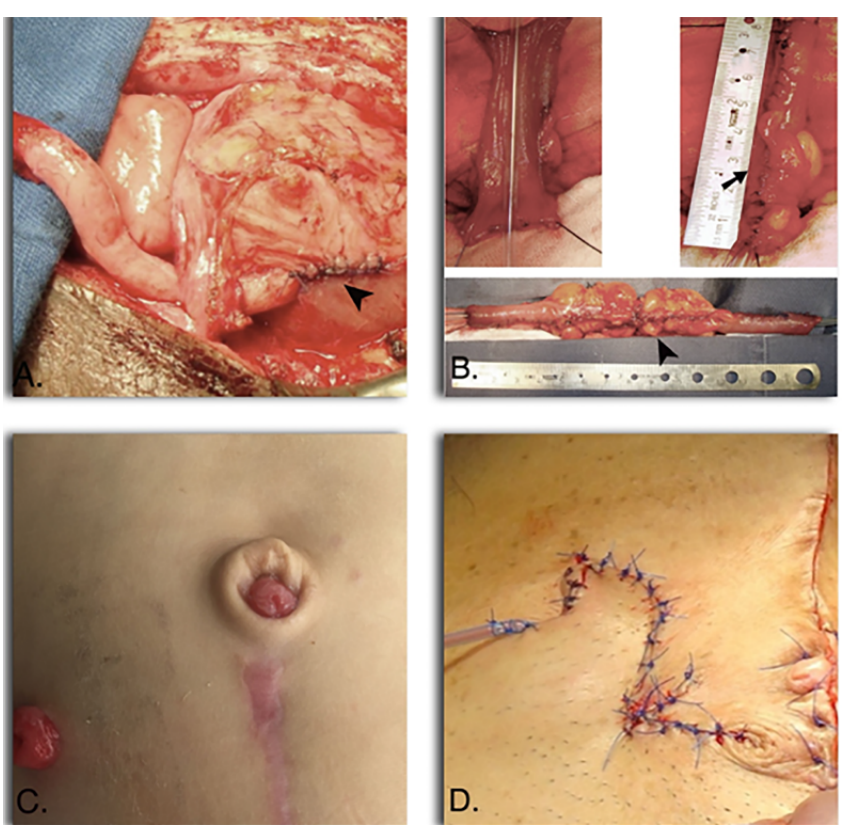
INTRODUCTION

Paul Mitrofanoff described the "trans--appendicular continent cystostomy" in 1980, 8 years after Lapides described the clean intermittent catheterization technique (CIC) (1, 2). Both approaches have revolutionized the management of neurogenic bladder (1). Santiago Triana in 1947 have already

described a trans-appendicular continent reservoir, replacing the bladder with an isolated segment of the cecum, despite being the first author to describe it, his technique never became as popular as the Mitrofanoff principle (3). The CUD with the Mitrofanoff principle described a new concept where the bladder could be emptied by a route other than the urethra. This was of remarkable importance specially when the urethra could not be used, or the patient would require lifelong CIC. Initially the appendix was the only segment of bowel used and the bladder neck was usually closed. As the appendix is not always available, different techniques have been described over time with other intestinal segments but based on the Mitrofanoff principle (3). Some variations are the transverse ileal tube (Yang-Monti), the double tube (Monti technique) and the Casale (Monti Spiral technique) (Figure-1). There has also been reports of conduits constructed with fallopian tubes, gastric segments, ureter (hydroureter) and even tubularized preputial transverse island flaps which have all been abandoned (1-3, 5).

Indications for CUD with the Mitrofanoff principle are neurogenic bladder with or without urethral lengthening, bladder neck closure or augmentation cystoplasty when required, complex urethral strictures due to location, non-viable urethral reconstructive surgery or previous brachy-radiotherapy, bladder dysfunction with intact urethral sensation (Congenital Obstructive Posterior Urethral Membrane (COPUM), Prune Belly syndrome, bladder or cloacal exstrophy--epispadias complex and idiopathic dysfunctional bladder). The same principle could be applied to the Malone Antegrade Continence Enema (MACE) for intractable constipation (1, 4, 5).

Figure 1 - A) Appendicovesicostomy with the Mitrofanoff principle showing an anti-reflux extravesical reimplantation technique (arrow head) as the anti-incontinence mechanism. B) Continent urinary diversion with the Mitrofanoff principle using an ileal segment for a transverse ileal tube (Yang-Monti) (arrow) and a double tube (Monti technique) (arrow head). C) Umbilical Stoma in a patient who underwent an Appendicovesicostomy and Malone antegrade continence enema (MACE) procedure. D) V-Quadrilateral-Z (VQZ) plasty stoma in a patient with a complex urethral stricture.



The use of retrograde CIC causes considerable changes in patient's daily activities, modifying their social routine, professional activities and sexuality (6). In some cases, family members or caregivers who accompany the patient during treatment and are accountable for the performance of the CIC would also have an impact in HRQoL. Furmincelli, et al. evaluated 13 studies that reported on HRQoL in patients on CIC finding that patients on CIC presented lower QoL scores as well as their caregivers (6).

HRQoL in patients reliant upon Mitrofanoff catheterization had been reported to be good in most series (7, 8). Ease of catheterization had roughly been described in patients with CUD with the Mitrofanoff principle and had been more focused on the type of stoma (Umbilical, V-Quadrilateral-Z (VQZ) plasty (Figure-1) and V-Quadrilateral (VQ) flaps) being easy in most patients (5, 7). Cosmesis and satisfaction had been described to be satisfactory or excellent in most patients but doing emphasis on the type of stoma (1, 5, 7-9) The aim of this article is to determine HRQoL, ease of catheterization, and self-perception of global satisfaction and cosmetic outcomes in a subset of patients with CUD with the Mitrofanoff principle and to compare the results in patients with umbilical stomas and V-Quadrilateral-Z (VQZ) plasty stomas.

MATERIALS AND METHODS

After IRB approval, IRB number 20190415-755, records of all patients that underwent CUD with Mitrofanoff principle between 2012 to 2018 were reviewed. Data was collected and analysed retrospectively from medical charts. Each patient was invited to participate in our study and a fully signed informed consent was required to participate. A total of 22 patients out of 25 were contacted by phone (in order to get as many participants as possible we called each patient at least three times at different days or hours). For all patients that answered the phone-call, a cross-sectional design was used to evaluate HRQoL using the EuroQol EQ-5D-3L questionnaire. Approval from the EuroQol Research Foundation was granted. This is a 5-question health-related survey, each question with three possible answers assessing mobility, self-care, usual activities, pain or discomfort, anxiety and depression. Each of the five dimensions comprising the EQ-5D-3L descriptive system is divided into three levels of perceived problems (LEVEL 1: indicating no problem, LEVEL 2: indicating some problems, LEVEL 3: Indicating extreme problems). It also has a Visual analogue scale (VAS) to measure health status from 0 (the worst health you can imagine) to a 100 (the best health you can imagine) and it gives a EQ-VAS score (10, 11).

For pediatric patients it was a requisite that they were able to read and write in order to answer the questionnaire with adult assistance.

In order to assess cosmetic and functional outcomes we used a questionnaire designed by the members of the reconstructive urology division of the San Ignacio University Hospital (HUSI). This questionnaire included 5 questions with a YES/NO answer. To evaluate ease or difficulty of catheterization we adapted with help of the functional urology, neuro-urology and reconstructive urology divisions of the HUSI, the Questionnaire for Intermittent Catheterization Difficulty Questionnaire (ICDQ) which was validated to evaluate difficulty with catheterization in patients reliant on retrograde CIC (13). The final Likert Questionnaire is made of 5 questions with 4 answer options for each question (0-Never, 1-Infrequent, 2-Frequent and 3-Always).

RESULTS

Twenty-five patients requiring CUD with the Mitrofanoff principle between 2012 and 2018 were included in the study. Median follow-up was 57 months with an IQR of 9-84 months, median age was 30 years with an IQR of 5-76 years. Nineteen men and 6 women had surgery, the group was composed mainly of appendiceal conduits 18 patients (72%),7 ileal conduits (Yang-Monti) (28%), three of those requiring Casale (Monti Spiral) (12%) and one a Double tube (Monti technique). Diagnosis and indications for the procedure were complex urethral strictures in 12 (48%) patients, neurogenic bladder, 7 (28%), bladder or cloacal exstrophy and epispadias complex 4 (16%), one

(4%) Casamassima syndrome and complex recto--vesical fistula in one patient (4%). Seventeen (68%) patients had a flank VQZ stoma and 8 (32%) had an umbilical stoma. Seven patients were pediatric (younger than 18 years-old), with a mean age in this subgroup of 8.5 years. Regarding complications, there were 4 major complications in our study. Two were appendiceal conduit necrosis. One case had partial necrosis of the conduit that was re-tailored and successfully reconstructed 6 months after the initial surgery and the other case was a complete loss of the conduit, The patient finally opted for a suprapubic catheter. Two patients had urinary incontinence. One due to failure of the antireflux mechanism, which was solved by endoscopic bulking agent injection. The other patient had incontinence due to intrinsic sphincteric deficiency that required bladder neck closure. Both patients were dry at the time of the study. Three patients presented stomal stenosis and none of them required revision and were managed with indwelling catheters. A summary is presented in Table-1.

Table 1 - Revision and were managed with indwelling catheters.

Number of patients, *n*	25
Age (years)	Median 30, IQR (5-76)
Male:Female Rate	2.5:1
Stoma	
Flank VQZ	17
Umbilical	8
Surgical Technique n (%)	
Appendicovesicostomy	18 (72)
Ileal conduit (Yang- Monti)	6 ((24)
Double Ileal Tube (Monti)	1 (4)
Casale (Spiral Monti)	3 (12)
Primary Diagnosis and indication for CUD n (%)	
Spinal dysraphism	1 (4)
Exstrophy-Epispadias complex	2 (8)
Cloacal abnormality	2 (8)
Complex Urethral Stricture	12 (48)
Neurogenic Bladder	6 (24)
Recto-vesical fistula	1 (4)
Other (Casamassima Syndrome)	1 (4)
Complications n (%)	4 (16)
Conduit Necrosis	2 (8)
Incontinence	2 (8)
Stomal Stenosis	3 (12)
Follow-up (Months)	Median 57, IQR (9-84)

Of the 25 CUD patients, we were able to contact 22 (88%). One of the patients who could not be contacted had died of a cause other than the surgery. The other two could not be reached at the phone-number registered in the medical chart. HRQoL was assessed using the EQ-5D-3L Questionnaire. We found that 95% of our patients had no problems with mobility. Ninety one percent had no problems with self-care, 77% were able to do their usual activities and of the 23% that had some problems, only one blamed the surgery to be the cause. Eighty six percent had no pain or discomfort in daily activities and 14% did mention some sort of discomfort or pain in daily activities. We confirmed with the patients that the pain referred was not related to the CUD. Regarding anxiety and depression, 59% did not consider themselves anxious or depressed, while 41% said to be moderately anxious or depressed.

EQ VAS of the EQ-5D-3 reported a Global health score of 86.5%. Sixty eight percent reported their global health score to be between 80-100% and only one patient scored below 60%.

To evaluate ease of self-catheterization we use our own Likert Questionnaire. All of our patients including the pediatric subgroup, performed CIC by themselves without help of their caregivers. We found that 59% of the patients had no pain (the CIC wasn't painful), 41% of the patients had conduit bleeding with catheterization. Eighty two percent hadn't had residual pain after catheterization, 45.4% hadn't had a blocking sensation with catheterization, although 41% despite it was infrequent (1 point) complained about it and 13.6% said they frequently (2 points) had a transitory blocking sensation. Eighty two percent hadn't had a blocking sensation during catheter withdrawal (Table-2).

Forty one percent of patient's complaint of conduit bleeding infrequently and reported a blocking sensation while introducing the catheter, none of them had complaint about it in the follow-up visits despite having been asked. The blocking sensation while introducing the catheter could be explained as the sensation of overcoming the antireflux mechanism, because 82% did not have a blocking sensation during catheter withdrawal. Only 3 of 25 patients have had stomal stenosis and all cases resolved with conservative management.

Cosmetic and global satisfaction were assessed using a qualitative questionnaire designed by our group at the Reconstructive Urology Division of the HUSI. When asked, 73% of the patients would undergo CUD surgery with the Mitrofanoff principle again. A 91% satisfaction rate with their CUD was found. Ninety five percent of patients would not hesitate to recommend this kind of surgery to a friend or relative. Seventy seven percent of patients were satisfied with their body image when they dressed themselves and 64% were satisfied with their stomal appearance while 36% were unsatisfied (Table-2).

To evaluate differences in HRQoL, ease of catheterization, cosmetic and functional outcomes we performed a subgroup analysis comparing the eight patients with umbilical stoma against the seventeen patients with the VQZ-stoma. We found that patients in the umbilical stoma subgroup reported a mean EQ-VAS-score of 94 ± 6.48 compared to a mean EQ-VAS-score of 83.6 ± 14 in the VQZ-stoma. Difficulty with catheterization was similar in both groups. Satisfaction rates with the appearance of the stoma was lower in the umbilical stoma group without a clear explanation. Patients were more likely to have had an umbilical stoma when they were younger, no patient over 30 years-old at the time of surgery was chosen to have an umbilical stoma. Stomal stenosis or incontinence were complications not associated with the umbilical stoma group in our series.

DISCUSSION

Few studies have evaluated HRQoL, ease of catheterization, cosmetic and functional outcomes of CUD with the Mitrofanoff principle. Despite its qualitative nature, our study is one of the most complete studies addressing this subject, with a long term follow-up, a wide variety of diagnosis and different stoma tailoring techniques.

CUD with the Mitrofanoff principle aims to create a continent catheterizable conduit that is easily accessible to the patient's dominant hand (1, 4, 7, 13). Despite all the modifications of the technique, CUD with the Mitrofanoff principle

Table 2 - Mitrofanoff Catheterization Difficulty Questionnaire (HUSI) - Adapted from the ICDQ and Global Satisfaction and Cosmetic Outcomes Questionnaire (HUSI).

Mitrofanoff Catheterization Difficulty Questionnaire (HUSI) - Adapted from the ICDQ					
	0 (Never) N (%)	1 (Infrequent) N (%)	2 (Frequent) N (%)	3 (Always) N (%)	Total (n)
1 - Do I have pain, or the CIC is painful?	13 (59)	7 (32)	1 (4.5)	1 (4.5)	22
2 - Does your stoma bleed with CIC?	13 (59)	9 (41)	0 (0)	0 (0)	22
3 - Do I have residual pain after the catheterization?	18 (82)	4 (18)	0 (0)	0 (0)	22
4 - Do I experience a blocking sensation and some force is required to insert the catheter?	10 (45)	9 (41)	3 (13.6)	0 (0)	22
5 - Do I have a blocking sensation during catheter withdrawal?	18 (82)	3 (13.6)	1 (4.5)	0 (0)	22
Global Satisfaction and Cosmetic Outcomes Questionnaire (HUSI)					
	Yes N (%)		No N (%)		Total N (%)
1 - Knowing what you already know, would you undergo a continent urinary diversion again?	16 (73)		6 (27)		22 (100)
2 - Are you satisfied with your continent urinary diversion?	20 (91)		2 (9)		22 (100)
3 - Would you recommend this type of reconstruction to a friend with your same problem?	21 (95)		1 (5)		22 (100)
4 - Are you satisfied with your body image when getting dressed?	17 (77)		5 (23)		22 (100)
5 - Are you satisfied with your stomal appearance?	14 (64)		8 (36)		22 (100)

remains a complex procedure with a significant non-negligible complication rate (14). This surgical reconstruction technique has been described for pediatric and adult patients (15).

Our study includes a wide range of age groups, as well as, diverse pathologies which demonstrates that this surgery is an important resource in any age group to resolve obstructive, functional and anatomic problems of the urinary tract. In the pediatric subgroup the mean age was 8.5 years, all patients were able to self-perform CIC and none of them have had stomal stenosis or another major complication.

There is scarce information about quality of life in this population. Smith, et al. evaluated 19 patients older than 16-years-old with the SF-36 health survey Version 2®. The score for Physical Functioning (PF=50.4), Role Physical (RP=53.8), Bodily Pain (BP=55.6), Vitality (VT=56.9), Social Functioning (SF=51.5), Role Emotional (RE=52.2), and Mental Health (MH=54.6) were all higher than those reported within the normal population

(normal=50.0) and found the same results when compared against age-matched controls (9). This results are comparable with ours. We used a validated Questionnaire to assessed HRQoL, the EQ-5D-3L and the mean EQ VAS score was 86.5% which is comparable with the general population (8, 11). Lima, et al. evaluated HRQoL in patients with neurogenic bladder submitted to urological reconstructive surgeries: seven patients with cutaneous appendicovesicostomy, 1 continent cutaneous ileo-vesicostomy (Yang-Monti technique) and 1 patient with Malone antegrade continence enema (MACE) procedure. This study used the SF-36 Health Survey® and the Qualiveen® to measure patient reported outcomes measure (PROMs) and found improvement in all domains with statistical significance (8).

Few studies have evaluated ease or difficulty of catheterization in patients with CUD with the Mitrofanoff principle. Because of the lack of a validated questionnaire to assess difficult catheterization we decided to use the ICDQ questionnaire. It was developed by Guinet-Lacoste et al. in France, and validated in 70 patients with neurogenic bladder reliant on retrograde CIC (12).

They found a good internal correlation and a good test-retest correlation with an ICC of 0.81 and a cronbach alpha of 0.94 (12).

Self-perception and functional impact of the stoma is an important factor for children's and adults. It is traditionally located at the right flank or the umbilicus and the stomal site and technique of construction has received as much attention and variation as the Mitrofanoff principle itself. Some authors suggest the best stoma tailoring technique is the VQ instead of the VQZ (16, 17). The latter results in a more prominent and irregular scar with the same complication rate or stoma continence (12, 14, 18, 19). In our study 17 stomas were tailored with the VQZ technique and 8 were umbilical stomas. Decisive factors for localization and type of stoma were length and mobility of the appendix mesentery. We found that 36% are unsatisfied with their stomal appearance, although we are under the impression that most of these patients were unhappy due to having to live with a stoma rather than with the cosmetic appearance of it.

Gowda, et al. evaluated the outcome of the Mitrofanoff stoma in 65 patients with a mean follow up of 75.2 months, 30 patients underwent a bladder-neck procedure at the same time of CUD. Difficulty catheterizing occurred in 46%, whilst 8% suffered stomal incontinence (18). Eleven stomal dilations and 38 skin level stomal corrections were performed. Overall, 97% of patients still had a catheterizable channel, which was continent in 95% (18). Sahadevan, et al. audited the long-term outcome of 29 adult patients with a Mitrofanoff CUD, with a mean follow-up 126 months. Of those 71% had an appendicovesicostomy and the remaining an ileal conduit (Yang-Monti). An 89% continence rate was reported. Stomal stenosis occurred in 54% of the stomas. Conversion to an ileal conduit was required in 18% of patients, two for persistent incontinence and three for recurrent stomal complications (19). In our study we found a 12% stomal stenosis rate and 100% were continent after bulking agent injection in one patient, and bladder neck closure in another one. One of the longest follow-up series in CUD with the Mitrofanoff principle was presented by Liard, et al., with a 20-year follow-up of their patients. This study showed that 16 of 23 patients still had a catheterizable and continent stoma and 9 patients had stomal stenosis despite all efforts to prevent it (20).

Despite all efforts in modifying the technique, stomal stenosis remains the most common complication reported in the literature, with a rate of stenosis of 6 to 39%. We found a 12% rate of stomal stenosis, all successfully managed with conservative measures and all of the stomal stenosis complications in the subgroup of the flank VQZ stoma. Other more serious complications where partial and total necrosis of the appendiceal conduit, retrospectively we think the length of the appendix mesentery wasn't enough for building the catheterizable conduit. These complications have already been reported in other series but every effort should be made to prevent them (4, 14).

The limitations of our study are the cross-sectional design and retrospective nature of it, as well as reporting outcomes of pediatric and

adult patients. Some of the questionnaires were not designed or validated in pediatric population but given the heterogeneity of our population we decided to use one questionnaire for evaluating HRQoL. A prospective design measuring PROMs before and after surgery would help to resolve many questions remaining in the CUD surgery.

CONCLUSION

Continent urinary diversion with the Mitrofanoff principle is associated with a good HR-QoL, ease of catheterization in most patients, remarkable global satisfaction with the procedure and adequate self-perception of the cosmetic results. It remains a safe and viable option for children and adults who have the indication, with a low complication rate and need for re-intervention. The umbilical stoma patients had better quality of life scores compared with V-Quadrilateral--Z (VQZ) plasty, despite having lower satisfaction rates with the appearance of the stoma. Stomal stenosis or incontinence were complications not associated with the umbilical stoma group in our series, despite being reported on other articles.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Farrugia MK, Malone PS. Educational article: The Mitrofanoff procedure. J Pediatr Urol. 2010;6:330-7.
2. Lapides J, Diokno AC, Silber SJ, Lowe BS. Clean, Intermittent Self-Catheterization in the Treatment of Urinary Tract Disease. J Urol. 2017;197(2S):S122-S124.
3. Cortes ST. Nueva tecnica de exclusion de la vejiga utilizando el clego aislado como receptaculo. Rev. Fac. Med. 1947;15: 577-616.
4. Harris CF, Cooper CS, Hutcheson JC, Snyder HM 3rd. Appendicovesicostomy: the mitrofanoff procedure-a 15-year perspective. J Urol. 2000;163:1922-6.
5. Landau EH, Gofrit ON, Cipele H, Hardak B, Duvdevani M, Pode D, et al. Superiority of the VQZ over the tubularized skin flap and the umbilicus for continent abdominal stoma in children. J Urol. 2008;180(4 Suppl):1761-5; discussion 1765-6.
6. Fumincelli L, Mazzo A, Martins JCA, Henriques FMD, Cardoso D, Rodrigues MA. Quality of Life of Intermittent Urinary Catheterization Users and Their Caregivers: A Scoping Review. Worldviews Evid Based Nurs. 2017;14:324-333.
7. Itesako T, Nara K, Matsui F, Matsumoto F, Shimada K. Clinical experience of the VQZ plasty for catheterizable urinary stomas. J Pediatr Urol. 2011;7:433-7.
8. Lima DX, Pires CR, Santos AC, Mendes RG, Fonseca CE, Zocratto OB. Quality of life evaluation of patients with neurogenic bladder submitted to reconstructive urological surgeries preserving the bladder. Int Braz J Urol. 2015;41:542-6.
9. Smith GM, Carroll D, Mukherjee S, Aldridge R, Jayakumar S, McCarthy L, et al. Health-related quality of life in patients reliant upon mitrofanoff catheterisation. Eur J Pediatr Surg. 2011;21:263-5.
10. Santos M, Cintra MA, Monteiro AL, Santos B, Gusmão-Filho F, Andrade MV, et al. Brazilian Valuation of EQ-5D-3L Health States: Results from a Saturation Study. Med Decis Making. 2016;36:253-63.
11. Herdman M, Badia X, Berra S. [EuroQol-5D: a simple alternative for measuring health-related quality of life in primary care]. Aten Primaria. 2001;28:425-30.
12. Siegel S, Noblett K, Mangel J, Griebling TL, Sutherland SE, Bird ET, et al. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourol Urodyn. 2015;34:224-30.
13. England RJ, Subramaniam R. Functional and cosmetic outcome of the VQ plasty for Mitrofanoff stomas. J Urol. 2007;178:2607-10.
14. Cain MP, Casale AJ, King SJ, Rink RC. Appendicovesicostomy and newer alternatives for the Mitrofanoff procedure: results in the last 100 patients at Riley Children's Hospital. J Urol. 1999;162:1749-52.
15. Ramanan V, Kapoor R, Srinadh ES, Babu R, Ramanathan R, Kumar A. Mitrofanoff principle for continent urinary diversion. Urol Int. 1997;58:108-12.
16. McAndrew HF, Malone PS. Continent catheterizable conduits: which stoma, which conduit and which reservoir? BJU Int. 2002;89:86-9.
17. Berrettini A, Rigamonti W, Castagnetti M. Modified VQZ-plasty for the creation of a catheterizable stoma suitable as a neoumbilicus in selected bladder exstrophy patients. Urology. 2008;72:1073-6.

18. Gowda BD, Agrawal V, Harrison SC. The continent, catheterizable abdominal conduit in adult urological practice. BJU Int. 2008;102:1688-92.
19. Sahadevan K, Pickard RS, Neal DE, Hasan TS. Is continent diversion using the Mitrofanoff principle a viable long-term option for adults requiring bladder replacement? BJU Int. 2008;102:236-40.
20. Liard A, Séguier-Lipszyc E, Mathiot A, Mitrofanoff P. The Mitrofanoff procedure: 20 years later. J Urol. 2001;165(6 Pt 2):2394-8.

Correspondence address:
Julián Chavarriaga. MD
Division of Urology,
Hospital Universitario San Ignacio, Pontificia Universidad Javeriana
Carrera 7 / 40-62
Bogotá, Colombia
Fax: +57 1 320-8320
E-mail: chavarriagaj@javeriana.edu.co

EDITORIAL COMMENT

Vol. 46 (5): 752-753, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0388.1

Editorial Comment: Self-perception, quality of life and ease of catheterization in patients with continent urinary diversion with the mitrofanoff principle

Antonio Carlos Moreira Amarante [1]

[1] *Departamento de Cirurgia Pediátrica, Hospital Pequeno Príncipe, Curitiba, PR, Brasil*

COMMENT

The Mitrofanoff principle came to meet the needs of patients and urologists at the seventies decade. It made easier the intermitent self catheterization by the neurological impaired patients stablishing a way to empty the bladder without the need of a huge mobilization specially for the wheelchair bound patients or their caregivers.

As the numbers of proceedings raised, the numbers of complications went up too. This is well related in most of the papers published about the Mitrofanoff technique.

The high numbers of complications made us think about the satisfaction or dissatisfaction with the procedure and what is the quality of life of these patients . Very little has been done in this sense. I found only one paper at PUbMed with the analysis of the quality of life of these patients (1). This has a similar number of subjects but it only uses the SF36® health survey V2 that measures 8 health concepts compared against published data for the normal population. Their results are similar to the paper presented by the authors.

The paper describes the satisfaction of the patients in respect to the stoma, in spite of the relatively high numbers of small complications that may have needed surgical treatment or medical attention.

In the present paper the sample is small (22 patients), the ages have a big interval variation (5 to 76 years), the follow up varies from 8 to 84 months and the basic diagnosis of the patients varies between neurogenic bladder, urethral strictures,extrophy, cloacal anomalies and other diagnossis (2). This may be a draw back on the analysis of the answers because the patients may be in diferent phases of life, may have diferent sensibility and may have different body image making the sample not very homogeneous.

Anyway, the most importante information is that 95% of the patients would recommend the procedure to a friend or to somebody with the same problem.

This may need more studies with more numbers and a more homogeneous sample to have definitive answers. This paper may be a kick off on this direction.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Smith GM, Carroll D, Mukherjee S, Aldridge R, Jayakumar S, McCarthy L, et al. Health-related quality of life in patients reliant upon mitrofanoff catheterisation. Eur J Pediatr Surg. 2011;21:263-5.
2. Chavarriaga J, Fernández N, Campo MAO, Bolivar J, Patiño G, Perez J. Self-perception, quality of life and ease of catheterization in patients with continent urinary diversion with the mitrofanoff principle. Int Braz J Urol. 2020;46:743-51.

Antonio Carlos Moreira Amarante, MD

Departamento de Cirurgia Pediátrica,
Hospital Pequeno Príncipe,
Curitiba, PR, Brasil
E-mail: antonio.amarante@gmail.com

ARTICLE INFO

Antonio Carlos Moreira Amarante
https://orcid.org/0000-0003-4167-0257

Int Braz J Urol. 2020; 46: 752-3

Submitted for publication:
April 25, 2020

Accepted:
May 10, 2020

ORIGINAL ARTICLE

Vol. 46 (5): 754-771, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0420

Comparison and trend of perioperative outcomes between robot-assisted radical prostatectomy and open radical prostatectomy: nationwide inpatient sample 2009-2014

Yingyi Qin [1], Hedong Han [1], Yongping Xue [2], Cheng Wu [1], Xin Wei [3, 4], Yuzhou Liu [3], Yang Cao [5, 6], Yiming Ruan [1], Jia He [1, 7]

[1] Department of Health Statistics, Second Military Medical University, Shanghai, China; [2] Department of Urology, Changhai Hospital, Second Military Medical University, Shanghai, China; [3] Mount Sinai St. Luke's and West Medical Center, New York, USA; [4] Department of Cardiology, Virginia Commonwealth University, Richmond, USA; [5] Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [6] Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden; [7] Tongji University School of Medicine, Shanghai, China

ABSTRACT

Purpose: To make a further evaluation of perioperative outcomes between the robot-assisted radical prostatectomy (RARP) and open radical prostatectomy (ORP), we conducted a comparison and trend analysis by using the Nationwide Inpatient Sample (NIS) from 2009 to 2014.

Materials and Methods: Adult prostate cancer patients with radical prostatectomy were abstracted from the NIS. RARP and ORP were identified according to the International Classification of Diseases, 9th Revision, Clinical Modification procedure codes. The perioperative outcomes included blood transfusion, intraoperative and postoperative complications, prolonged length of stay (pLOS), and in-hospital mortality. Propensity score matching method and multivariable logistic regression model were performed to adjust for the pre-defined covariates. The annual percent change (APC) was used to detect the change trend of rates for outcomes.

Results: A total of 77.054 patients were included in our study. According to the results of propensity score matching analyses, RARP outperformed ORP in blood transfusion (1.96% vs. 9.40%), intraoperative complication (0.73% vs. 1.25%), overall postoperative complications (8.87% vs. 11.97%), and pLOS (13.39% vs. 36.70%). We also found that there was a significant decreasing tendency of incidence in blood transfusion (APC=-9.81), intraoperative complication (APC=-12.84), and miscellaneous surgical complications (APC=-14.09) for the RARP group. The results of multivariable analyses were almost consistent with those of propensity score matching analyses.

Conclusions: The RARP approach has lower incidence rates of perioperative complications than the ORP approach, and there is a potential decreasing tendency of complication incidence rates for the RARP.

ARTICLE INFO

Jia He
http://orcid.org/0000-0002-2338-9501

Keywords:
Prostatic Neoplasms; Prostatectomy; Robotics

Int Braz J Urol. 2020; 46: 754-71

Submitted for publication:
June 28, 2019

Accepted after revision:
August 16, 2019

Published as Ahead of Print:
October 30, 2019

INTRODUCTION

Prostate cancer (PCa) is one of the most common solid organ cancer in men, and accounts for about 20% of all cancers diagnosed (1). For localized PCa, the surgery with radical prostatectomy (RP) is the dominant approach (2). RP could be performed by open or minimally invasive approach. According to the Prostate Cancer Guidelines provided by European Association of Urology (EAU), there is no recommendation for the surgical approach choice among open, laparoscopic and robot-assisted approaches (3). The robot-assisted radical prostatectomy (RARP), which was first reported by Binder and Kramer in 2001, is becoming the dominant surgical approach for RP (4). In the United States, more than 60 percent of RPs had been performed through robot-assisted approach in 2009 (5).

About the pros and cons of RARP, several studies had found that RARP was associated with reductions in some intraoperative and postoperative complications when compared with open radical prostatectomy (ORP) (5-7). RARP was also reported to reduce the possibility of blood transfusions and shorten the length of stay in hospital. However, some researchers thought that RARP and ORP had comparable rates of operative complications (8-10). A randomized controlled trail (RCT) had shown that minimally invasive benefits were seen in the RARP group and both approaches yielded similar functional outcomes at 12 weeks and 2 years (11, 12). These previous studies had provided some useful but conflicting information about the comparison between these two surgical approaches. Further evidence should be based on the larger population study, and the trend of comparison results along with the development and wide application of RARP need to be investigated. The aim of our study was to make further evaluation of comparison of perioperative complication rates between RARP and ORP and investigate the trend of perioperative complication rates for these two approaches using six years of Nationwide Inpatient Sample (NIS) data (2009-2014).

MATERIALS AND METHODS

Data source

The database used in this study was based on inpatient discharge data obtained from the NIS of the Healthcare Cost and Utilization Project (HCUP). A robot-assisted modifier code was introduced and received approval by the US Food and Drug Administration (FDA) to identify robot--assisted procedures in October 1, 2008. Therefore, we chose sample population from all of NIS inpatient discharge data from January 2009 to December 2014. Detailed information on NIS data is available at <http://www.hcup-us.ahrq.gov>. The NIS is a deidentified database so institutional review board approval is not required.

Patients and surgical approach

Adult patients (older than 18 years) with a primary diagnosis of PCa were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 185.0. The surgical approaches were classed according to the ICD-9-CM procedure codes. All PCa patients with radical prostatectomy were selected (ICD-9-CM 60.5). The RARP group was defined as PCa patients who underwent the robotic assisted procedures (ICD-9-CM 17.4x). The ORP group was defined as patients who underwent RA without the robotic assisted procedures and laparoscopy procedures (ICD-9-CM 54.21).

Demographic characteristics

The following demographic characteristics of each patient were abstracted from the database: age, year of surgery (2009-2014), race, Elixhauser Comorbidity Index (ECI), insurance status. The ECI includes 29 disease conditions and might be a useful way to control for confounding in cancer outcomes research (13, 14). Hospital-related characteristics were also included in our study: location, academic status, region, control/ownership of hospital, bed size of hospital.

Outcomes

Intraoperative complications: The intraoperative complications were identified according to ICD-9-CM code 998.2 suggested by previous

study (5), and included accidental puncture or laceration during surgery.

Postoperative complications: We included seven categories of complications (Cardiac, Respiratory, Genitourinary, Wound, Vascular, Miscellaneous medical, and Miscellaneous surgical) using ICD-9-CM code provided by Hu et al. (7, 15).

Homologous blood transfusion: We identified patients with blood transfusion using ICD-9-CM procedure codes 99.02 and 99.04.

Prolonged length of stay (pLOS): The pLOS was defined as length of stay beyond the 75th percentile (2 days).

In-hospital mortality: The information of in-hospital mortality was abstracted from "DIED" variable.

Statistical analysis

Descriptive statistics were summarized for the demographic characteristics of the RARP group and the ORP group. Median (interquartile range, IQR) was calculated for age, and counts (percentages) were calculated for other categorical variables. We conducted the comparison of demographic characteristics between two groups by using Wilcoxon Rank Sum test, Chi-square test, or Cochran-Mantel-Haenszel (CMH) test.

We conducted the propensity score matching method to balance the covariates between the RARP group and the ORP group. The logistic regression model was performed to calculate the propensity score based on all covariates described in above demographic characteristics. The RARP and ORP group were matched based on the logit of the propensity score by using the calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score (16). The odds ratios (OR) and corresponding 95% confidence interval (CI) of RARP compared with ORP for each perioperative outcome were calculated by using univariate logistic regression in matched cohort and using multivariable logistic regression model adjusted for all demographic characteristics in non-matched cohort.

We used the annual percent change (APC) to investigate the trend of rate change for blood transfusion, pLOS, intraoperative and postoperative complication, from 2009 to 2014, respectively (17). Similar to the overall analyses shown above, we also calculated the ORs of each year for these perioperative outcomes. To detect the change trend of ORs, we constructed the annual ratio change (ARC) based on the theory of APC calculation. For example, if the ARC is 1.01, and the OR is 1.05 in 2009, the OR is 1.05×1.01=1.06 in 2010. The APC over 0 and the ARC over 1 represent a trend of increase, and on the contrary represent a trend of decrease.

All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC), and the statistical figures were drawn by using R software. All reported p values were two-sided and a p value <0.05 was regarded as statistically significant.

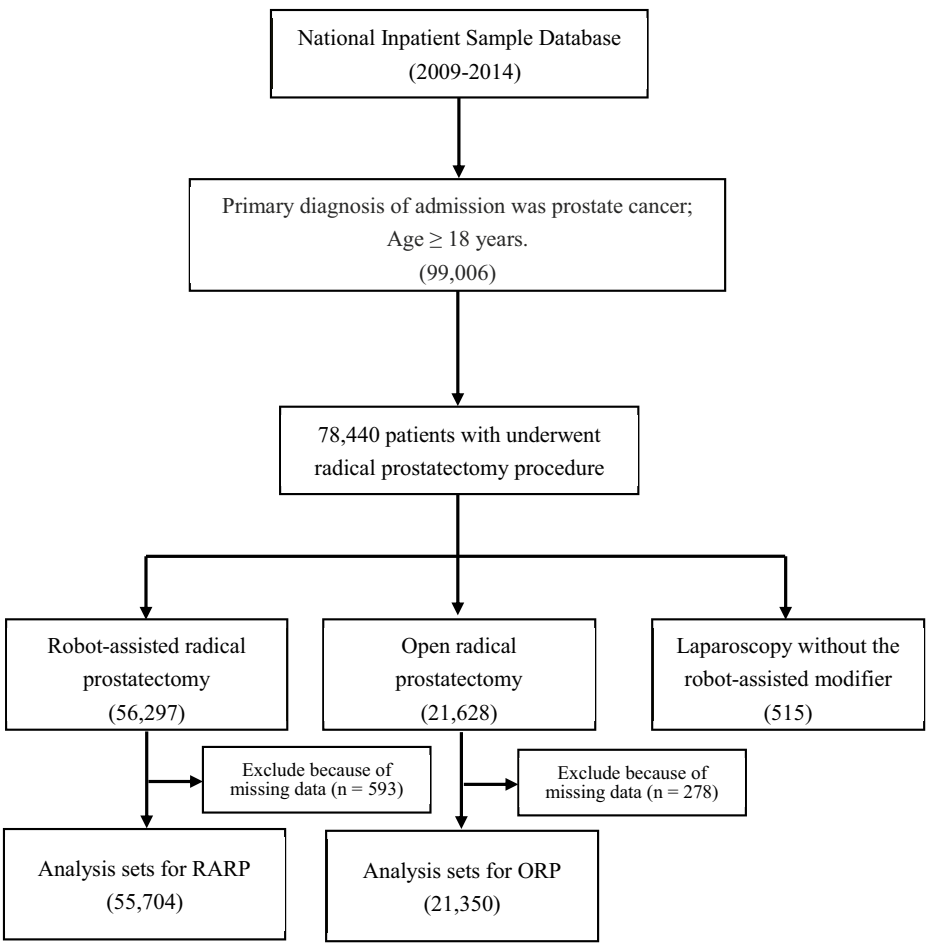
RESULTS

Demographic characteristics

Among a total of 99.006 adult patients with primary diagnosis of PCa between 2009 and 2014, 78,440 patients underwent radical prostatectomy procedure. There were 55.704 patients with RARP approach and 21.350 patients with ORP approach (Figure-1).

According to the distribution of demographic characteristics, we found that the number of patients with ORP approach had reduced from 2009 to 2014. The proportion of RARP on white was higher than that of ORP (68.69% vs 66.24%), and more black patients underwent ORP approach (10.58% vs. 12.48%). Greater proportion of the RARP group had no comorbidities than the ORP group (for ECI of 0: 34.51% vs. 32.41%). With regard to the hospital-related characteristics, we found that RARP approach would be more likely to be performed in urban (97.89% vs. 91.19%, p <0.0001) and teaching (72.67% vs. 59.75%, p <0.0001) hospitals than ORP approach. There was statistical significant difference on all of the characteristics between the RARP group and the ORP group, and the baseline covariates were much more balanced after conducting the propensity score matching procedure. Further details of demographic characteristics before and after matching are listed in Table-1.

Figure 1 - The flow chart of patients selection.



Perioperative outcomes

The information of comparison for perioperative outcomes between the RARP group and the ORP group are shown in Table-2. The results of pre-propensity score-matched cohort and post--propensity score-matched cohort were consistent. According to the results of propensity score matching analyses, we found that the RARP group had significant lower rates of almost all of the pre-defined complications and outcomes than the ORP group except vascular complication (0.40% vs. 0.52%, OR=0.77, 95% CI: 0.58-1.03, p=0.0802). The results indicated that patients with RARP had lower incidence rate for blood transfusion (1.96% vs. 9.40%, p <0.0001), intraoperative complication (0.73% vs. 1.25%, p <0.0001), and overall postoperative complications (8.87% vs. 11.97%, p <0.0001). Additionally, the RARP group also had shorter LOS (for pLOS, 13.39% vs. 36.70%, p <0.0001).

The trends of perioperative outcomes from 2009 to 2014

We provided the rate of pre-defined outcomes for each year from 2009 to 2014 in Figure-2 (post-propensity score-matched cohort) and supplementary Figure-1 (pre-propensity score-

-matched cohort). The results of post-propensity score-matched cohort showed that the rates of these outcomes in the RARP group were consistent lower than the ORP group among most years. The results of trend analyses indicated that there were significant decreases in homologous blood transfusion (APC=-9.81, p=0.0060), intraoperative complication (APC=-12.84, p=0.0214), and miscellaneous surgical (APC=-14.09, p=0.0015) for the RARP group, and only in homologous blood transfusion (APC=-6.80, p=0.0404) for the ORP group. The significant trend of decrease was also found in pLOS (APC=-2.19, p=0.0422) for the RARP group within the pre-propensity score-matched cohort (Table-3).

Figure-3 presents the forest plots to show the ORs (RARP vs. ORP) and corresponding 95% CI of outcomes in each year for post-propensity score-matched cohort (supplementary Figure-2 for pre-propensity score-matched cohort). The most of the OR point estimates was smaller than one for the outcomes within each year, and this indicated that the PCa patients with RARP approach would have lower risk to these complications and outcomes than patients with ORP approach. We also found the persistent significant lower risk for the RARP group in blood transfusion, overall postoperative complications, respiratory, and pLOS compared with the ORP group. According to the results of trend analyses for ORs before and after propensity score matching, there might be a potential trend of decrease in miscellaneous surgical (before matching, ARC=0.92, 95% CI: 0.85-1.00, p=0.0525; after matching, ARC=0.89, 95% CI: 0.78-1.02, p=0.0775, Table-3).

DISCUSSION

The NIS database showed that the proportion of the RARP approach for PCa patients was increasing year by year in the United States, from about 60% in 2009 to about 80% in 2014. To provide further evidence for the comparison between the RARP and ORP approaches, we compared the incidence rate of pre-defined complications and outcomes between two groups by using the inpatient data form 2009 to 2014. The results indicated that the RARP group had lower rates in most of complications except vascular complication. Additionally, we also found that there were significant decreasing trend of incidence rates in blood transfusion and some surgical injuries for the RARP group, such as intraoperative complications and miscellaneous surgical complications.

According to several previous studies, they had provided reliable evidence to indicate that the RARP approach outperformed the ORP approach in blood loss and hospital stay (5, 7). The results of our study were consistent with previous finding and we further found these two superiorities in each year. With regard to the intraoperative and postoperative complications, Trinh et al. had shown that superior outcomes were seen in the RARP group, especially for intraoperative complication, cardiac, and respiratory (5), and Hu et al. had also demonstrated that fewer miscellaneous surgical complications were found in men undergoing minimally invasive RP (7). In our study, the comparison of perioperative complications between two groups showed that the RARP group had lower rates of all pre-defined complications and the significant statistical differences were detected except in vascular complication. Actually, we should notice that the incidence rates for most of these perioperative complications might be not much high in both of two surgical approaches and the absolute difference between two groups was small (e.g. only 0.22% for wound complication). The reason of large sample size for overall analyses (the information from a total of 6 years) should be taken into account for the significant statistical difference between two groups. Additionally, the results of comparison within each year had also provided the evidence to suggest the superiority of RARP approach in perioperative complications.

To explore the tendency for the rates of complications from 2009 to 2014, we calculated the APC for the RARP group and the ORP group, respectively. We found that most of APCs were less than zero for both the RARP group and the ORP group, and this had indicated a potential trend of decrease about the perioperative complications for these two surgical approaches. According to the statistical test for APC, there was significant statistical decrease tendency in blood transfusion, intraoperative complication and miscellaneous

Table 1 - Demographic characteristics of patients treated with radical prostatectomy for prostate cancer.

	Pre-propensity score-matched			Post-propensity score-matched		
	RARP (N=55704)	ORP (N=21350)	p value	RARP (N=20573)	ORP (N=20573)	p value
Age, year, median (IQR)	62 (57-67)	62 (57-67)	0.0086	62 (57-67)	62 (57-67)	0.9041
Year of surgery, n (%)						
2009	9608 (17.25)	5450 (25.53)	<0.0001	5089 (24.74)	5154 (25.05)	0.2171
2010	8819 (15.83)	4410 (20.66)		4064 (19.75)	4190 (20.37)	
2011	11338 (20.35)	4858 (22.75)		4713 (22.91)	4683 (22.76)	
2012	8978 (16.12)	2556 (11.97)		2510 (12.20)	2503 (12.17)	
2013	8661 (15.55)	2192 (10.27)		2193 (10.66)	2171 (10.55)	
2014	8300 (14.90)	1884 (8.82)		2004 (9.74)	1872 (9.10)	
Race, n (%)						
white	38261 (68.69)	14142 (66.24)	<0.0001	13699 (66.59)	13650 (66.35)	0.6484
black	5894 (10.58)	2665 (12.48)		2560 (12.44)	2543 (12.36)	
Hispanic	3099 (5.56)	1207 (5.65)		1098 (5.34)	1176 (5.72)	
Asian or Pacific Islander	914 (1.64)	273 (1.28)		251 (1.22)	273 (1.33)	
Native American	281 (0.50)	72 (0.34)		67 (0.33)	68 (0.33)	
other	1915 (3.44)	533 (2.50)		540 (2.62)	519 (2.52)	
missing	5340 (9.59)	2458 (11.51)		2358 (11.46)	2344 (11.39)	
ECI, n (%)						
0	19226 (34.51)	6920 (32.41)	<0.0001	6704 (32.59)	6711 (32.62)	0.9440
1	20383 (36.59)	7584 (35.52)		7357 (35.76)	7345 (35.70)	
2	10795 (19.38)	4391 (20.57)		4216 (20.49)	4233 (20.58)	
≥3	5300 (9.51)	2455 (11.50)		2296 (11.16)	2284 (11.10)	
Insurance status, n (%)						
Medicare	18452 (33.13)	6923 (32.43)	<0.0001	6567 (31.92)	6643 (32.29)	0.8146
Medicaid	1110 (1.99)	695 (3.26)		655 (3.18)	634 (3.08)	
Private insurance	34084 (61.19)	12549 (58.78)		12219 (59.39)	12179 (59.20)	

Continued

	Pre-propensity score-matched			Post-propensity score-matched		
	RARP (N=55704)	ORP (N=21350)	p value	RARP (N=20573)	ORP (N=20573)	p value
Other	2058 (3.69)	1183 (5.54)		1132 (5.50)	1117 (5.43)	
Hospital location, n (%)						
Rural	1175 (2.11)	1881 (8.81)	<0.0001	1168 (5.68)	1179 (5.73)	0.8151
Urban	54529 (97.89)	19469 (91.19)		19405 (94.32)	19394 (94.27)	
Hospital academic status, n (%)						
Nonteaching	15224 (27.33)	8594 (40.25)	<0.0001	7872 (38.26)	7835 (38.08)	0.7073
Teaching	40480 (72.67)	12756 (59.75)		12701 (61.74)	12738 (61.92)	
Hospital region, n (%)						
Northeast	10554 (18.95)	4020 (18.83)	<0.0001	3930 (19.10)	3885 (18.88)	0.7744
Midwest	13407 (24.07)	5337 (25.00)		5090 (24.74)	5109 (24.83)	
South	19380 (34.79)	7893 (36.97)		7619 (37.03)	7572 (36.81)	
West	12363 (22.19)	4100 (19.20)		3934 (19.12)	4007 (19.48)	
Control/ownership of hospital, n (%)						
Government, nonfederal	5289 (9.49)	2154 (10.09)	<0.0001	2074 (10.08)	2023 (9.83)	0.6162
Private, non-profit	45613 (81.88)	16855 (78.95)		16254 (79.01)	16331 (79.38)	
Private, invest-own	4802 (8.62)	2341 (10.96)		2245 (10.91)	2219 (10.79)	
Bed size of hospital, n (%)						
Small	7682 (13.79)	2266 (10.61)	<0.0001	2219 (10.79)	2232 (10.85)	0.1593
Medium	12244 (21.98)	4622 (21.65)		4354 (21.16)	4522 (21.98)	
Large	35778 (64.23)	14462 (67.74)		14000 (68.05)	13819 (67.17)	t

RARP=Robot-assisted Radical Prostatectomy; **ORP**=Open Radical Prostatectomy; **IQR**=Interquartile Range; **ECI**=Elixhauser Comorbidity Index.

Table 2 - Perioperative outcomes during hospitalization of patients treated with RARP and ORP.

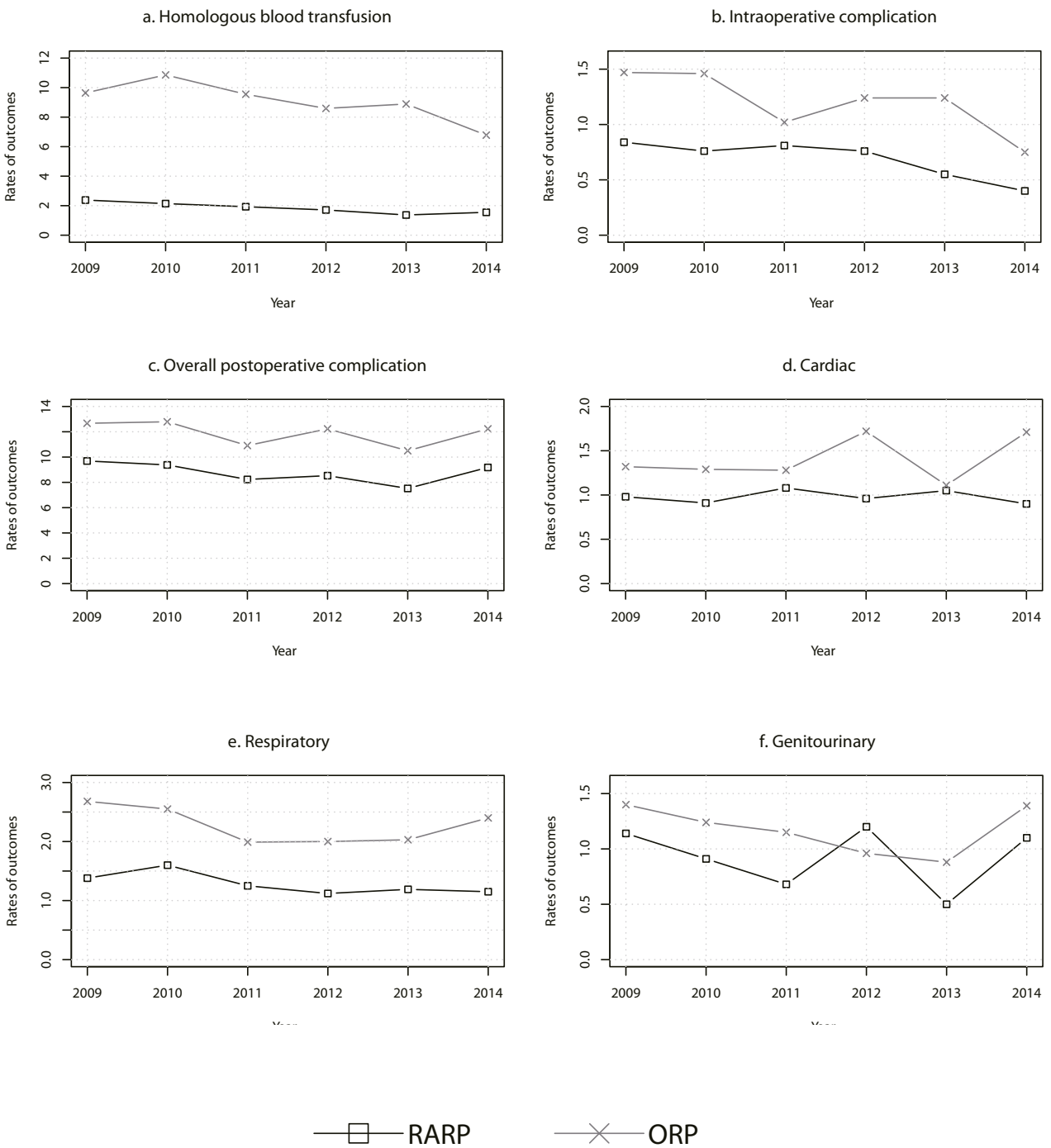
	Pre-propensity score-matched				Post-propensity score-matched			
	RARP (N=55704)	ORP (N=21350)	RARP vs. ORP OR (95% CI)*	p value	RARP (N=20573)	ORP (N=20573)	RARP vs. ORP OR (95% CI)#	p value
Homologous blood transfusion	896 (1.61)	2032 (9.52)	0.18 (0.16-0.19)	<0.0001	403 (1.96)	1934 (9.40)	0.19 (0.17-0.21)	<0.0001
Intraoperative complication	385 (0.69)	266 (1.25)	0.62 (0.52-0.73)	<0.0001	151 (0.73)	257 (1.25)	0.58 (0.48-0.72)	<0.0001
Postoperative complication								
Overall	4502 (8.08)	2576 (12.07)	0.71 (0.68-0.75)	<0.0001	1825 (8.87)	2463 (11.97)	0.72 (0.67-0.76)	<0.0001
Cardiac	513 (0.92)	292 (1.37)	0.75 (0.65-0.88)	0.0003	203 (0.99)	281 (1.37)	0.72 (0.60-0.86)	0.0004
Respiratory	640 (1.15)	508 (2.38)	0.57 (0.50-0.64)	<0.0001	271 (1.32)	477 (2.32)	0.56 (0.48-0.65)	<0.0001
Genitourinary	491 (0.88)	259 (1.21)	0.78 (0.67-0.92)	0.0023	190 (0.92)	247 (1.20)	0.77 (0.63-0.93)	0.0063
Wound	198 (0.36)	133 (0.62)	0.66 (0.52-0.83)	0.0004	84 (0.41)	130 (0.63)	0.64 (0.49-0.85)	0.0018
Vascular	210 (0.38)	110 (0.52)	0.82 (0.64-1.04)	0.1052	82 (0.40)	106 (0.52)	0.77 (0.58-1.03)	0.0802
Miscellaneous medical	2678 (4.81)	1400 (6.56)	0.80 (0.74-0.85)	<0.0001	1070 (5.20)	1338 (6.50)	0.79 (0.73-0.86)	<0.0001
Miscellaneous surgical	917 (1.65)	591 (2.77)	0.67 (0.60-0.74)	<0.0001	395 (1.92)	567 (2.76)	0.69 (0.61-0.79)	<0.0001
Length of stay >2d	6610 (11.87)	7956 (37.26)	0.25 (0.24-0.26)	<0.0001	2755 (13.39)	7551 (36.70)	0.27 (0.25-0.28)	<0.0001
In-hospital mortality	11 (0.02)	14 (0.07)	0.28 (0.12-0.63)	0.0021	3 (0.01)	14 (0.07)	0.21 (0.06-0.75)	0.0154

RARP=Robot-assisted Radical Prostatectomy; **ORP=**Open Radical Prostatectomy; **OR=**Odds Ratio; **CI=**Confidence interval.

Note: *The ORs and corresponding 95% CI for perioperative outcomes were estimated by using multivariable Logistic regression adjusted for demographic characteristics.

#The ORs and corresponding 95% CI for perioperative outcomes were estimated by using univariate Logistic regression.

Figure 2 - The incidence rates of the perioperative outcomes for the Robot-assisted Radical Prostatectomy group and the Open Radical Prostatectomy group from 2009 to 2014 (post-propensity score-matched cohort).



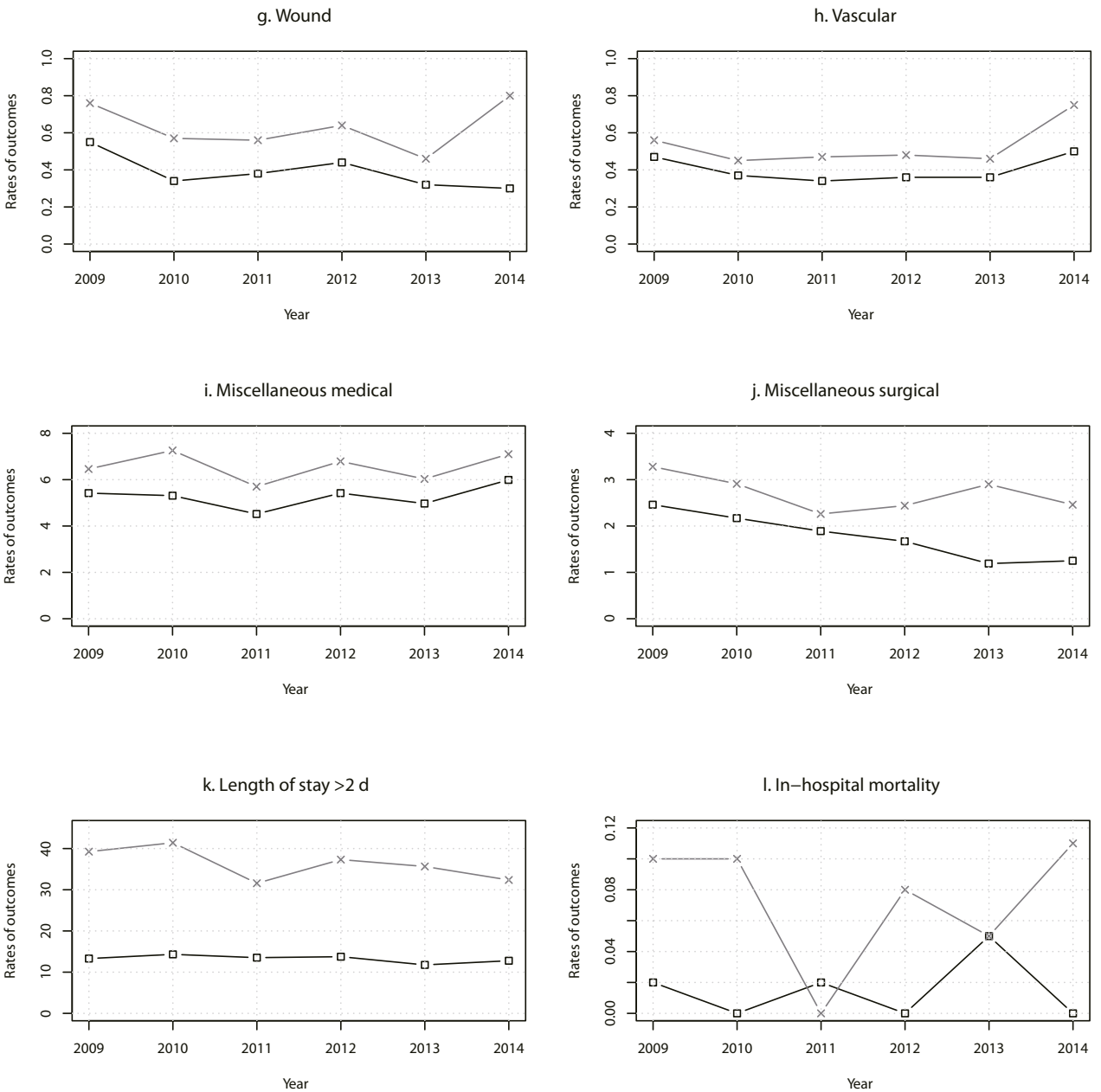
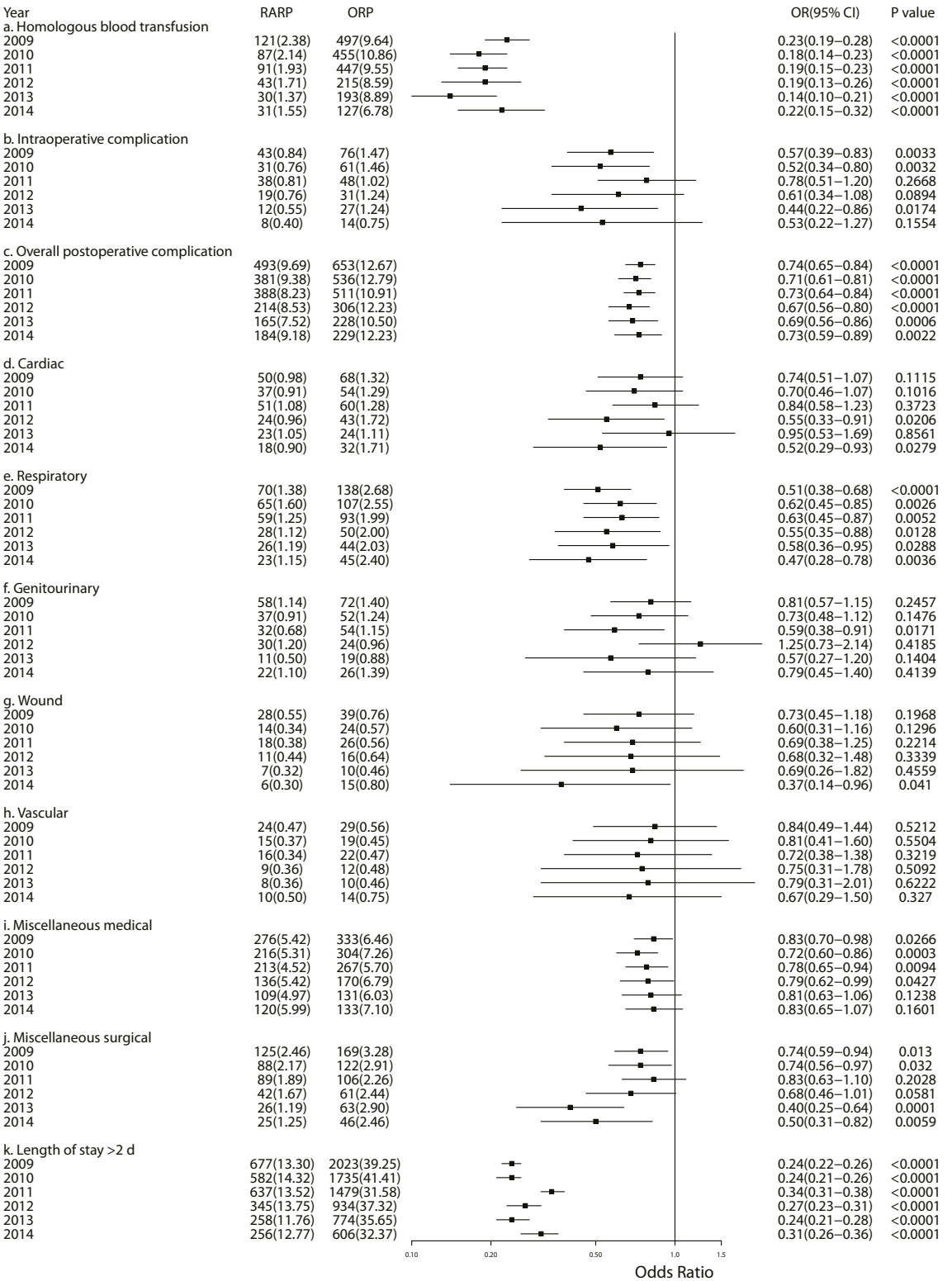

g. Wound
h. Vascular
i. Miscellaneous medical
j. Miscellaneous surgical
k. Length of stay >2 d
l. In–hospital mortality
Rates of outcomes
Year
2009
2010
2011
2012
2013
2014
RARP
ORP

Table 3 - The trend of change for the perioperative outcomes from 2009 to 2014.

	RARP		ORP		ARC (95% CI)	p value
	APC (95% CI)	p value	APC (95% CI)	p value		
Pre-propensity score-matched						
Homologous blood transfusion	-13.07 (-17.43, -8.49)	0.0016	-7.06 (-13.26, -0.42)	0.0421	0.94 (0.89, 0.98)	0.0224
Intraoperative complication	-10.08 (-13.64, -6.37)	0.0019	-10.15 (-20.00, 0.91)	0.0627	1.01 (0.91, 1.14)	0.7461
Postoperative complication						
Overall	-1.20 (-5.16, 2.92)	0.4580	-1.94 (-6.82.3.21)	0.3482	1.00 (0.98, 1.03)	0.6953
Cardiac	2.02 (-4.37, 8.84)	0.4391	2.75 (-8.92, 15.92)	0.5659	0.99 (0.81, 1.20)	0.8482
Respiratory	-3.86 (-9.05, 1.63)	0.1204	-3.84 (-12.01, 5.09)	0.2878	1.00 (0.91, 1.09)	0.9657
Genitourinary	-4.08 (-16.37, 10.02)	0.4468	-2.61 (-14.89, 11.45)	0.6154	1.01 (0.88, 1.16)	0.8780
Wound	-8.76 (-18.46, 2.10)	0.0864	-0.59 (-14.54, 15.65)	0.9193	0.90 (0.77, 1.06)	0.1571
Vascular	5.13 (-5.24, 16.63)	0.2522	5.07 (-6.82, 18.48)	0.3164	1.00 (0.83, 1.20)	0.9706
Miscellaneous medical	1.88 (-3.28, 7.31)	0.3767	0.12 (-5.93, 6.57)	0.9590	1.00 (0.98, 1.03)	0.7788
Miscellaneous surgical	-11.57 (-12.94, -10.17)	<0.0001	-3.90 (-11.95, 4.88)	0.2747	0.92 (0.85, 1.00)	0.0525
Length of stay >2d	-2.19 (-4.21, -0.13)	0.0422	-3.91 (-9.45, 1.98)	0.1362	1.03 (0.99, 1.07)	0.1136
Post-propensity score-matched						
Homologous blood transfusion	-9.81 (-14.54, -4.81)	0.0060	-6.80 (-12.70, -0.50)	0.0404	0.97 (0.86, 1.10)	0.5673
Intraoperative complication	-12.84 (-21.44, -3.29)	0.0214	-9.97 (-20.23, 1.60)	0.0734	0.97 (0.85, 1.11)	0.5499
Postoperative complication						
Overall	-2.52 (-8.24, 3.55)	0.3062	-1.85 (-7.11, 3.71)	0.4002	0.99 (0.97, 1.02)	0.5198
Cardiac	-0.42 (-5.77, 5.23)	0.8422	3.28 (-8.66, 16.77)	0.5066	0.96 (0.82, 1.14)	0.5783
Respiratory	-5.33 (-11.34, 1.07)	0.0808	-3.44 (-11.55, 5.40)	0.3292	0.98 (0.90,1.06)	0.4981
Genitourinary	-3.95 (-25.16, 23.28)	0.6772	-3.54 (-15.68, 10.34)	0.4981	1.00 (0.81, 1.23)	0.9671
Wound	-8.56 (-18.25, 2.27)	0.0907	-0.65 (-14.74, 15.77)	0.9121	0.92 (0.79, 1.06)	0.1819
Vascular	0.87 (-10.42, 13.58)	0.8500	4.35 (-8.51, 19.01)	0.4194	0.97 (0.93, 1.01)	0.0866
Miscellaneous medical	1.37 (-5.28, 8.48)	0.6076	0.28 (-6.49, 7.54)	0.9177	1.01 (0.97, 1.05)	0.4743
Miscellaneous surgical	-14.09 (-18.66, -9.26)	0.0015	-3.86 (-12.04, 5.08)	0.2861	0.89 (0.78, 1.02)	0.0775
Length of stay >2d	-2.19 (-6.04, 1.81)	0.1999	-3.50 (-9.28, 2.65)	0.1850	1.03 (0.93, 1.14)	0.4681

RARP=Robot-assisted Radical Prostatectomy; **ORP**=Open Radical Prostatectomy; **APC**=Annual Percent Change; **ARC**=Annual Ratio Change; **CI**=Confidence interval

Figure 3 - The forest plot of odds ratios for the comparison between Robot-assisted Radical Prostatectomy group with the Open Radical Prostatectomy group from 2009 to 2014 (post-propensity score-matched cohort).



surgical for the RARP group. However, we only found significant statistical decrease tendency in blood transfusion for the ORP group. With respect to the three outcomes in the RARP group shown above, they could reflect that the injury related to the operative procedures was decreasing with the popularity of the RARP approach. However, the methods for reducing the rates of some potentially life-threatening complications, such as cardiac, respiratory, and vascular events, might be the future research direction.

Among post-propensity score-matched cohort, the results of ARC had shown that the point estimates for most of outcomes were less than 1. The small ARCs indicated that the ORs of the RARP group compared with the ORP group might be becoming smaller as the year went on, and it might also suggest that the superiority of the RARP approach become slightly obvious. Aboud et al. had suggested that the learning curve for RARP (about 100 cases) was shorter than for ORP (ranged from 250 to 1000 cases) to reduce complication rates (18). This might be a potential reason to explain the increase of advantage for RARP with the popularity of this approach.

This study was based on the inpatient information and several limitations should be considered. First, the absence of follow-up information would be a drawback to make the comprehensive evaluation for the RARP. We focused on comparing the rates and exploring the change tendency of the perioperative complications between the RARP and ORP. Several previous studies had provided some information about functional outcome, such as urinary function and sexual function (11, 12, 19, 20). Additionally, the information of mortality in our study only represented the incidence of death during the period of hospitalization. Second, we did not conduct the comparison of the cost, and there were two reasons for the lack of analyses for cost: a, we could not abstract the accurate spending which was directly related to the surgical approach; b, the adjustment of actual value for dollars within each year from 2009 to 2014 might be another challenge (21). Third, although we conducted propensity score matching method to control the bias of the acquired covariates, several unobserved confounding factors, such as stage and pathologic characteristics of cancer, the characteristics of surgeon, and the determinants of patients, should be taken into account as sources of potential bias in our study.

CONCLUSIONS

In conclusion, our study had provided further evidence to indicate the superiority of the RARP approach in the perioperative outcomes compared to the ORP approach. The results of trend analyses indicated that there was a decreasing tendency of incidence rates for most of perioperative complications among patients underwent the RARP approach, especially for some surgical injuries related to the operative procedures. Furthermore, we concluded that the strategy for reducing potential life-threatening complications should be further investigated.

ABBREVIATIONS

APC = annual percent change
ARC = annual ratio change
C = confidence interval
CMH = Cochran-Mantel-Haenszel
EAU = European Association of Urology
ECI = Elixhauser Comorbidity Index
FDA = Food and Drug Administration
HCUP = Healthcare Cost and Utilization Project
ICD-9-CM = International Classification of Diseases 9th Revision, Clinical Modification
IQR = interquartile range
NIS = Nationwide Inpatient Sample
OR = odds ratios
ORP = open radical prostatectomy
pLOS = Prolonged length of stay
RARP = robot-assisted radical prostatectomy
RCT = randomized controlled trail
RP = radical prostatectomy
PCa = Prostate cancer.

FUNDING

This study was conducted under a grant from the National Key R&D Program of China (No.

2017YFC0908005), the Fourth Round of Shanghai Three-year Action Plan on Public Health Discipline and Talent Program: Evidence-based Public Health and Health Economics (No. 15GWZK0901), and Shanghai Sailing Program (No. 18YF1429500).

ACKNOWLEDGEMENTS

Yingyi Qin, Hedong Han, Yongping Xue, contributed similarly as first author

CONFLICT OF INTEREST

None declared.

REFERENCES

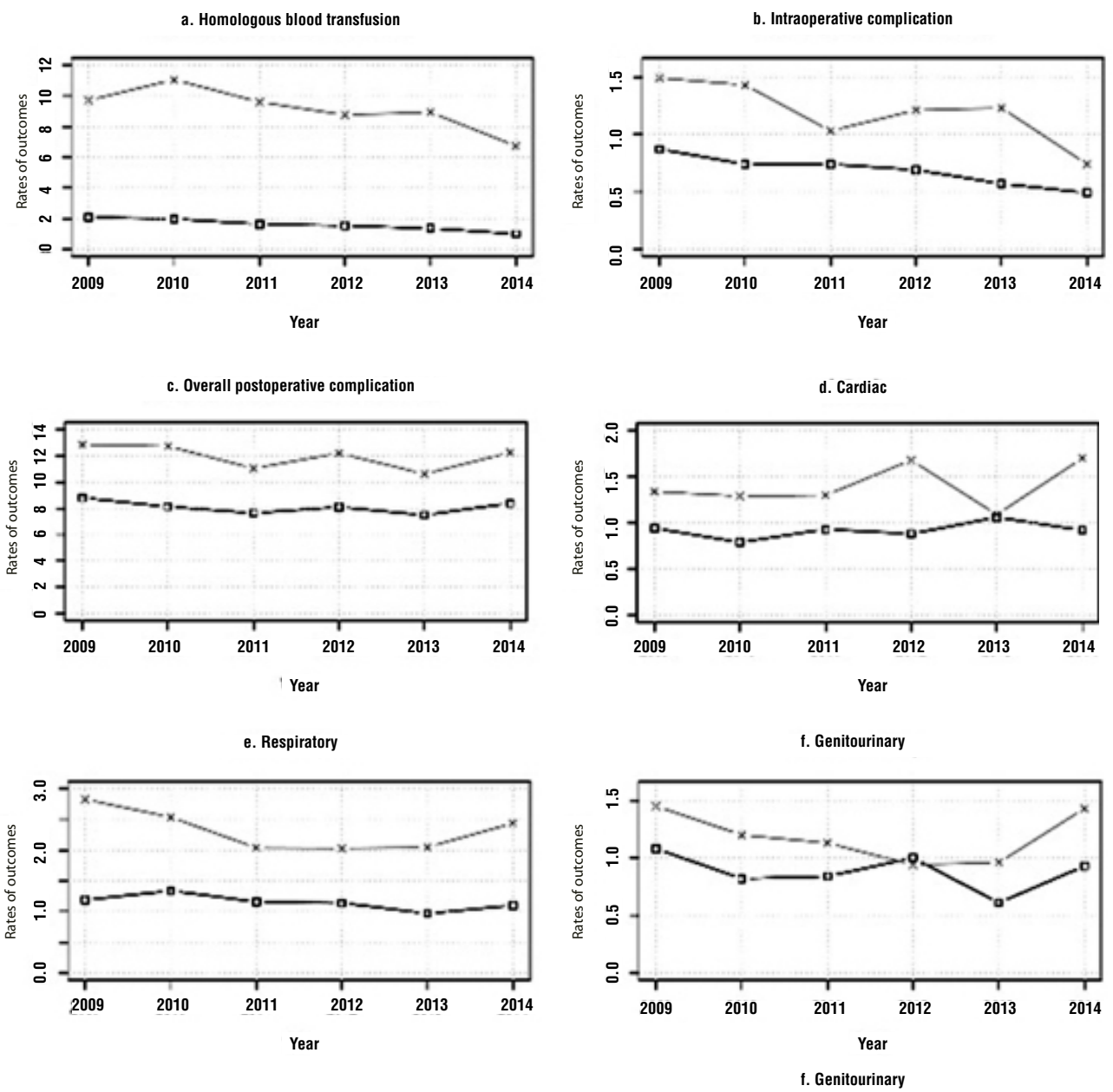
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7-30.
2. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367:203-13. Erratum in: N Engl J Med. 2012;367:582.
3. Hess CN, Kaltenbach LA, Doll JA, Cohen DJ, Peterson ED, Wang TY. Race and Sex Differences in Post-Myocardial Infarction Angina Frequency and Risk of 1-Year Unplanned Rehospitalization. Circulation. 2017;135:532-43.
4. Binder J, Kramer W. Robotically-assisted laparoscopic radical prostatectomy. BJU Int. 2001;87:408-10.
5. Trinh QD, Sammon J, Sun M, Ravi P, Ghani KR, Bianchi M, et al. Perioperative outcomes of robot-assisted radical prostatectomy compared with open radical prostatectomy: results from the nationwide inpatient sample. Eur Urol. 2012;61:679-85.
6. Pearce SM, Pariser JJ, Karrison T, Patel SG, Eggener SE. Comparison of Perioperative and Early Oncologic Outcomes between Open and Robotic Assisted Laparoscopic Prostatectomy in a Contemporary Population Based Cohort. J Urol. 2016;196:76-81.
7. Hu JC, Gu X, Lipsitz SR, Barry MJ, D'Amico AV, Weinberg AC, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. JAMA. 2009;302:1557-64.
8. O'Neil B, Koyama T, Alvarez J, Conwill RM, Albertsen PC, Cooperberg MR, et al. The Comparative Harms of Open and Robotic Prostatectomy in Population Based Samples. J Urol. 2016;195:321-9.
9. Pompe RS, Beyer B, Haese A, Preisser F, Michl U, Steuber T, et al. Postoperative complications of contemporary open and robot-assisted laparoscopic radical prostatectomy using standardised reporting systems. BJU Int. 2018;122:801-7.
10. Gandaglia G, Sammon JD, Chang SL, Choueiri TK, Hu JC, Karakiewicz PI, et al. Comparative effectiveness of robot-assisted and open radical prostatectomy in the postdissemination era. J Clin Oncol. 2014;32:1419-26.
11. Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet. 2016;388(10049):1057-1066. Erratum in: Lancet. 2017;389(10077):e5.
12. 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.
13. Austin SR, Wong YN, Uzzo RG, Beck JR, Egleston BL. Why Summary Comorbidity Measures Such As the Charlson Comorbidity Index and Elixhauser Score Work. Med Care. 2015;53:e65-72.
14. Mehta HB, Sura SD, Adhikari D, Andersen CR, Williams SB, Senagore AJ, et al. Adapting the Elixhauser comorbidity index for cancer patients. Cancer. 2018;124:2018-25.
15. Hu JC, Wang Q, Pashos CL, Lipsitz SR, Keating NL. Utilization and outcomes of minimally invasive radical prostatectomy. J Clin Oncol. 2008;26:2278-84.
16. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10:150-61.
17. Rosamond WD, Chambless LE, Folsom AR, Cooper LS, Conwill DE, Clegg L, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. N Engl J Med. 1998;339:861-7.
18. Abboudi H, Khan MS, Guru KA, Froghi S, de Win G, Van Poppel H, et al. Learning curves for urological procedures: a systematic review. BJU Int. 2014;114:617-29.

19. Ilic D, Evans SM, Allan CA, Jung JH, Murphy D, Frydenberg M. Laparoscopic and robot-assisted vs open radical prostatectomy for the treatment of localized prostate cancer: a Cochrane systematic review. BJU Int. 2018;121:845-53.
20. Ploussard G. Robotic surgery in urology: facts and reality. What are the real advantages of robotic approaches for prostate cancer patients? Curr Opin Urol. 2018;28:153-8.
21. Nguyen PL, Gu X, Lipsitz SR, Choueiri TK, Choi WW, Lei Y, et al. Cost implications of the rapid adoption of newer technologies for treating prostate cancer. J Clin Oncol. 2011;29:1517-24.

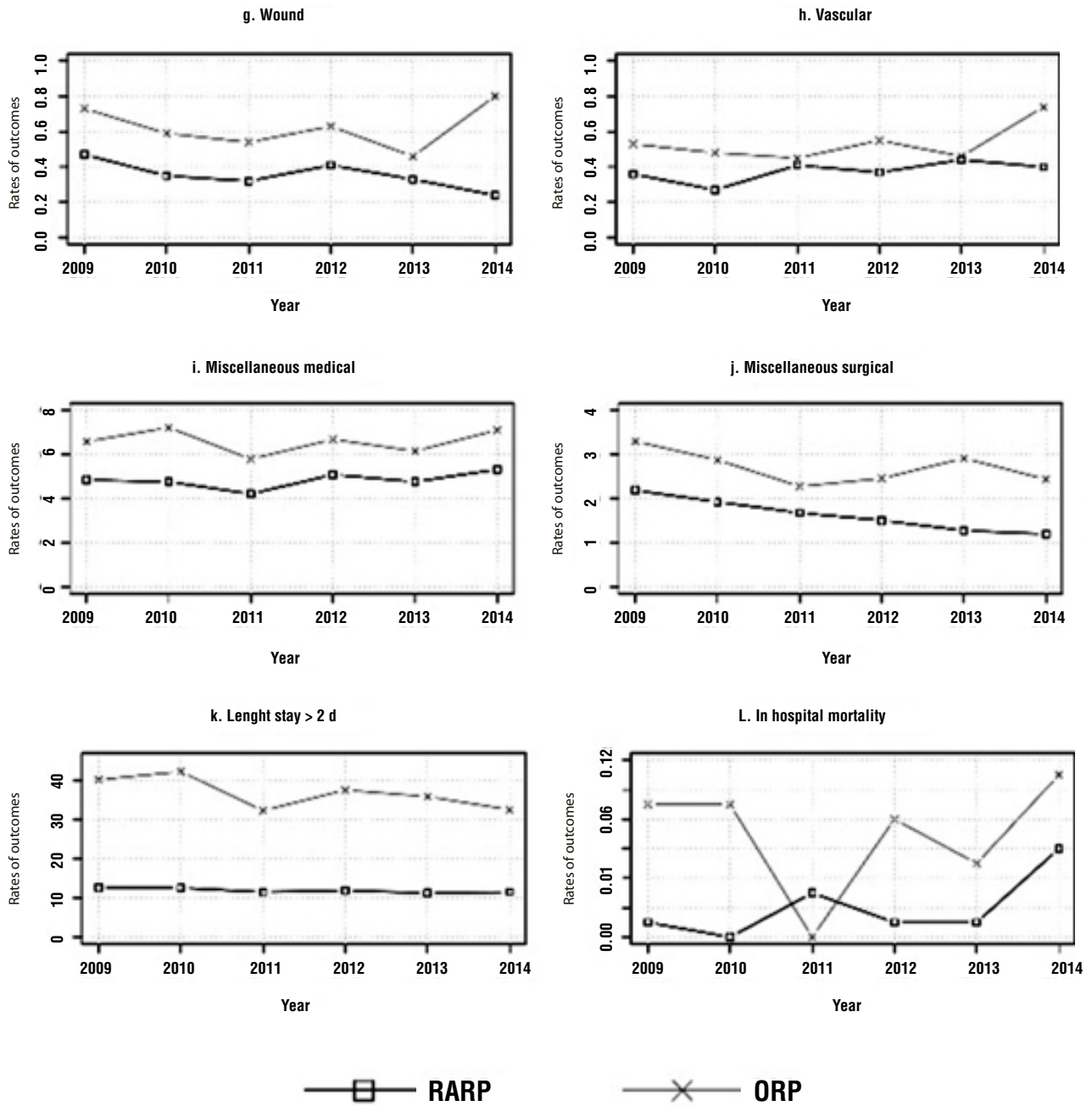
Correspondence address:
Jia He, PhD
Department of Health Statistics
Second Military Medical University
800 Xiangyin Road
Shanghai, 200433, China,
Telephone: + 86 81 871-441
E-mail: hejia63@yeah.net

APPENDIX -Supplementary Figures

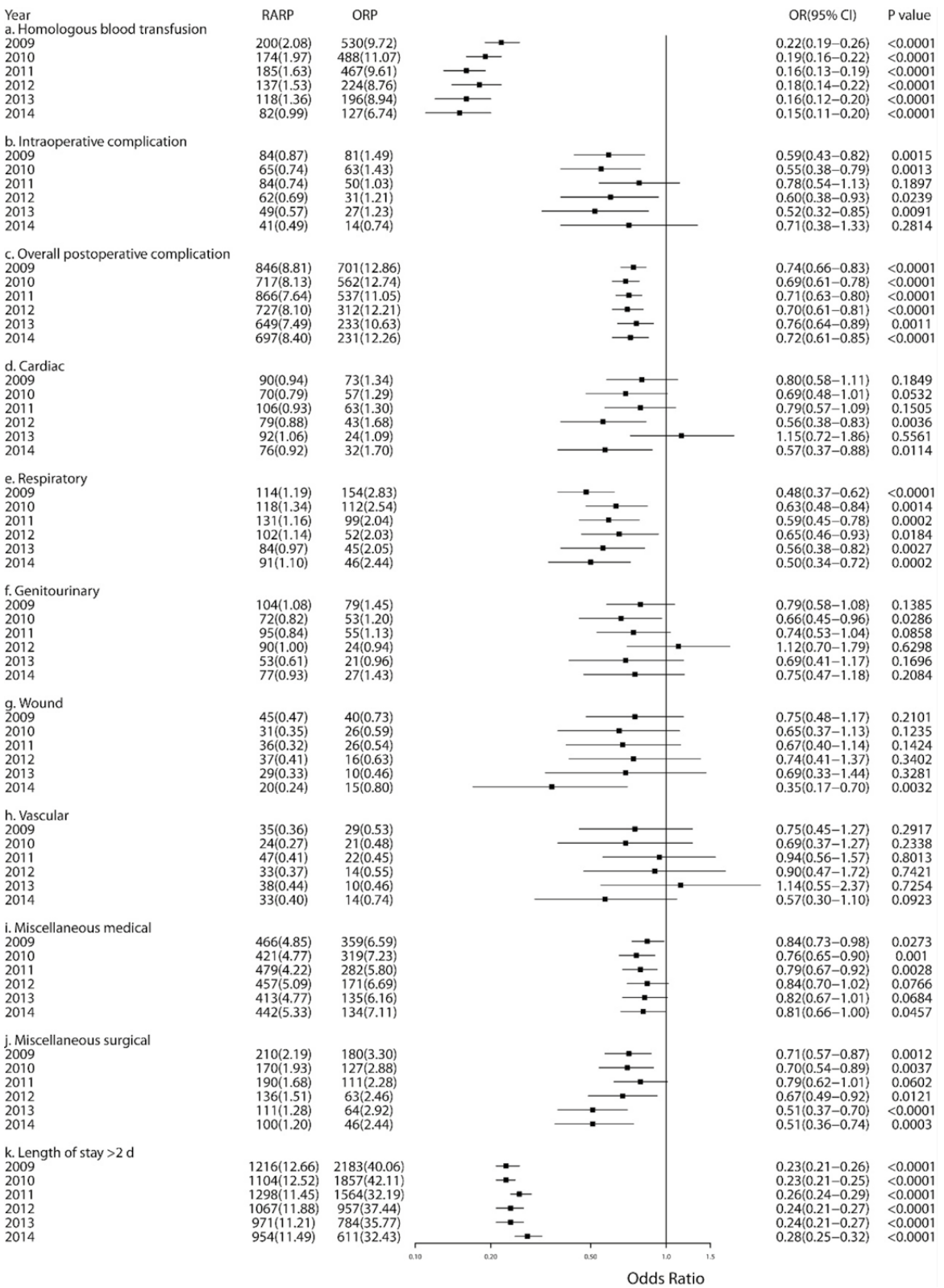
Supplementary Figure-1 - The incidence rates of the perioperative outcomes for the Robot-assisted Radical Prostatectomy group and the Open Radical Prostatectomy group from 2009 to 2014 (pre-propensity score-matched cohort).



f. Genitourinary


g. Wound
h. Vascular
i. Miscellaneous medical
j. Miscellaneous surgical
k. Lenght stay > 2 d
L. In hospital mortality
Rates of outcomes
Year
2009
2010
2011
2012
2013
2014
RARP
ORP

Supplementary Figure 2 - The forest plot of odds ratios for the comparison between Robot-assisted Radical Prostatectomy group with the Open Radical Prostatectomy group from 2009 to 2014 (pre-propensity score-matched cohort).



ORIGINAL ARTICLE

Vol. 46 (5): 772-777, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0484

Comparison of continuous eversion and inverting subepithelial suture in transverse preputial island flap urethroplasty in proximal hypospadias repair: A retrospective study

Wenwen Han [1], Weiping Zhang [2], Ning Sun [1], Yanfang Yang [1]

[1] Department of Urology, Beijing Children's Hospital Affiliated to Capital Medical University, Beijing, China; [2] Department of Urology, Children's hospital Affiliated to Zhengzhou University, Henan, China

ABSTRACT

Introduction: Transverse preputial island flap urethroplasty (TPIFU) is one of the most frequently performed technique for single-stage repair in proximal hypospadias. It was reported that the subepithelial urethroplasty would obviously decrease urethrocutaneous fistula (UF) complication after proximal TIP. But in the process of TPIFU, it had not been reported yet.

Objective: We reviewed our experience to evaluate and compare the effect of continuous eversion suture (CES) versus continuous inversion subepithelial suture (CIS) on complication rates in the TPIFU.

Material and methods: A retrospective review of all patients operated with CES and CIS in our institution between January 2017 and Jun 2017 was performed.

Results: A total of 161 patients were enrolled in the research. Patients were followed up for 12~17 months. Total success rate was 73.9% (119/161). No statistically difference was found between the two groups with regard to age of patients (P=0.097), catheter size (P=0.52), time of catheterization (P=0.47), length of neourethra (P=0.20), non-urethral comorbidity (P=0.44) and post-operative infection (P=1.0). The overall postoperative complications had no statistically difference between the two groups (P=0.067). There were no statistically significant differences in the incidence of urethra-cutaneous fistula (UF) (OR=0.07, 95% CI: -0.24~0.037, P=0.22), urethral diverticulum (UD) (OR=0.026, 95% CI: -0.16~-0.056, P=0.323), urethral stricture (US) (OR=0.081, 95% CI: -0.15~0.15, P=1.0) and breakdown of urethral repair (BU) (OR=0.02, 95% CI: -0.118~-0.044, P=1.0).

Discussion: The comparison of two group's postoperative complications was feasible because there were no statistically differences among perioperative variables. It seemed as if continuous inversion subepithelial suture would promote healing. However, it indicated that the overall success rate and the incidences of UF, UD, US and BU complications had no statistically difference between groups. It might be accounted for the subtle differences of techniques changing the process of establishing prime and side branches vascularization.

Conclusions: The CIS technique had no significantly different effect on the four complications rates when compared with CES in TPIFU. Thus, CES and CIS could be randomly adopted in TPIFU as personal preference.

ARTICLE INFO

Weiping Zhang
http://orcid.org/0000-0001-7999-5132

Keywords:
Surgical Flaps; Hypospadias; Wound Healing

Int Braz J Urol. 2020; 46: 772-7

Submitted for publication:
July 31, 2019

Accepted after revision:
November 14, 2019

Published as Ahead of Print:
April 10, 2020

INTRODUCTION

Proximal hypospadias remains one of the most challenging conditions for surgical correction and transverse preputial island flap urethroplasty (TPIFU) is one of the most frequently performed technique for single-stage repair (1, 2). But urethra-cutaneous fistula (UF), urethral diverticulum (UD), urethral stricture (US) and breakdown of urethral repair (BU) are the most common postoperative complications and the complication rates range from 14.6% to 37.9% (2). Many minimal modifications of TPIFU were invented to decrease the complications (3-5). However, the exact roles of these modifications in the successful outcome of hypospadias repair are yet to be determined. It was reported that the subepithelial urethroplasty would obviously decrease UF complication after proximal TIP (6), but in the process of TPIFU, whether it is effective to decrease surgical complications had not been reported before. In order to identify a better method, we reviewed our experience to evaluate and compare the effect of continuous eversion suture (CES) versus continuous inversion subepithelial suture (CIS) on complication rates in TPIFU.

MATERIALS AND METHODS

Patients primarily submitted to TPIFU in our department between January 1, 2017 and Jun 1, 2017 were retrospectively reviewed. Hypospadias performed by other techniques, preoperative testosterone injections and coverage of tunica vaginalis were all excluded. There was only one surgeon performing CIS, and others did CES in our hospital. All the patients were treated with standard TPIFU technique: A circumferential incision was made proximal to the corona and reached the depth of Buck's fascia. The dorsal skin was degloved toward the proximal penis. The urethral plate was transected to correct accompanying chordee completely, while if not, dorsal plication was performed. The meatus was dropped back to the proximal penis or the penoscrotal junction. The distance between the retracted meatus and the glans tip was measured to confirm the expected length of the neourethra. The rectangular flap was outlined at the inner aspect of the dorsal prepuce according to the length of the defect. The outlined foreskin was incised and rolled into a tube over a catheter and sutured with 6-0 absorbed PDS. The size of the catheter was chosen depended on the diameter of the patient's urethra and ranged between 6-Fr and 8-Fr. The tubularized neourethra was transposed ventrally through the glans channel and anastomosed with the native urethra with CIS or CES (according with the assigned group). The glans was incised deeply, the neourethra was placed and the new meatus was sutured on the top of the glans. The relaxed vascularized and de-epithelialized tissue was dissected to cover the neourethra. Finally, the foreskin was sutured together to cover all the penis.

We divided the patients into two groups according to the suture methods of the tubularized neourethra (continuous eversion suture group, Figure-1; group continuous inversion subepithelial suture group, Figure-2). All the urethral catheter used for drainage was kept for 2~6 weeks postoperatively to prevent stenosis. Venous antibiotics were applied for 3 to 5 days, oral antibiotics were continuously applied 1 week afterwards. Perioperative variables including the age of patients, catheter size, time of catheterization, length of neourethra, non-urethral comorbidity (yes or no) and postoperative infection (yes or no) were analyzed. The patients were followed-up for at least 6 months and postoperative complications of UF, UD, US and BU were recorded and analyzed. Surgical success was defined as no occurrence of these complications. The comparison between groups were analyzed using Chi-squared test and t test. All statistical calculations were performed by using SPSS 19.0. All tests were two-sided and P values <0.05 were considered significant. The research protocol was reviewed and approved by the Institutional Ethics Committee.

RESULTS

One hundred and seventy-five cases of proximal hypospadias operated with TPIFU were identified, fourteen were excluded as not meeting the screening criteria or lost to follow-up. Since there were several surgeons performing CES but

only one surgeon CIS, the number between two groups were quite imbalanced. Finally, 161 patients were included and divided into two groups:

Figure 1 - The tubularized neourethra was formed with continuous eversion suture and the anastomosing surface was rough.

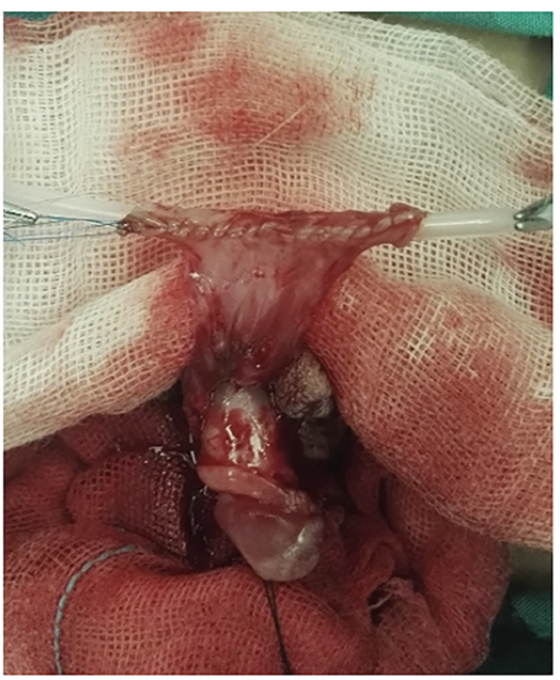
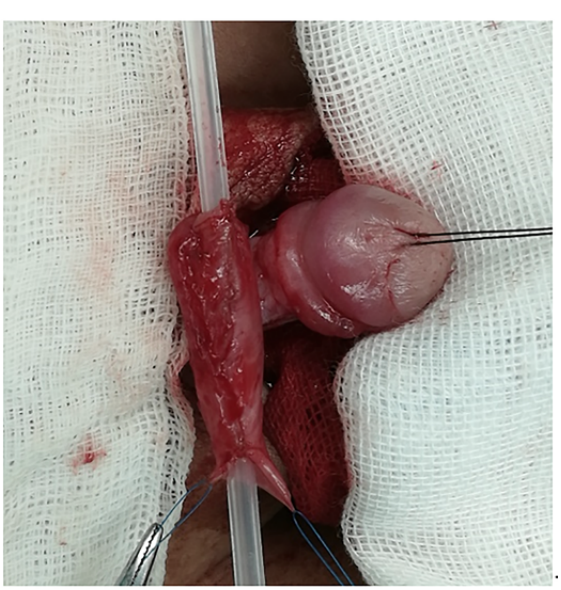


Figure 2 - The tubularized neourethra was formed with continuous inversion subepithelial suture and the anastomosing surface was smooth.



116 in CES group and 45 in CIS group. Age ranged from 1.17 to 15.5 years, with a mean of 5.8 and 5.1 years, respectively. Patients were followed for 12~17 months (mean 13.7 months). The total success rate was 73.9% (119/161). The success rate of CES group was 69.8% (81/116), and CIS group 84.4% (38/45). Non-urethral comorbidity were hernia, cryptorchid, hydrocele, penile-scrotal transposition and cardiac anomalies.

In univariable analysis, no statistically differences were found between the two groups with regard to the age of patients (P=0.097), catheter size (P=0.52), time of catheterization (P=0.47), length of neourethra (P=0.20), non-urethral comorbidity (P=0.44), and postoperative infection (P=1.0). There were no statistically differences among perioperative variables, so the imbalanced numbers between the two groups had little effect on the following results. Chi-squared test was used to compare the incidences of postoperative complications between the two groups. The overall postoperative complications had no statistical difference between the two groups (P=0.067). There were no statistically significant differences in the incidence of UF (OR=0.07, 95% CI: -0.24~0.037, P=0.22), UD (OR=0.026, 95% CI: -0.16~-0.056, P=0.323), US (OR=0.081, 95% CI: -0.15~0.15, P=1.0) and BU (OR=0.02, 95% CI: -0.118~-0.044, P=1.0). All the data and results of statistical analysis are shown in Tables 1 and 2.

DISCUSSION

The TPIFU was first described by Duckett in 1980 (7), it has been proven to be an efficient one-stage urethroplasty to correct proximal and severe chordee hypospadias (8). Although surgeons had been making various efforts or modifications to optimize the procedure, there are still certain complications and the best options for less complications are still debated. The purpose of all the minimal modifications was to provide a tension-free, well-vascularized tubularized neourethra and improve postoperative wound healing (2). The existing modifications were only designed to improve external condition, such as soft tissue interposition, removal, increase length and width of rectangular flap and in situ tubularization of

Table 1 - Characteristics of the CES and CIS groups and P values between them.

Risk factors	Range	CES	CIS	P
Age	1.17y~15.5y	5.87±3.28	5.13±3.03	0.097
Catheter size	6F	24	11	0.52
	8F	92	34	
Time of catheterization	2~6 w	4.15 ±0.91	3.74±0.63	0.47
Length of neourethra	1.5~8cm	3.73±1.34	3.92±1.13	0.20
Non-urethral comorbidity	No	102	37	0.44
	Yes	14	8	
Complications	No	81	38	0.067
	Yes	35	7	
The four complications	UF	21	4	0.55
	UD	5	0	
	US	8	3	
	BU	1	0	
Infection	No	106	41	1.0
	Yes	10	4	

CES = continuous eversion suture; **CIS** = continuous inversion subepithelial; **UF** = cutaneous fistula; **UD** = urethral diverticulum; **US** = urethral stricture and **BU** = breakdown of urethral repair

Table 2 - Chi-squared test among complications.

Complication	CES	CIS	P	OR	95% CI
UF					
No	95	41	0.22	0.07	-0.24~0.037
Yes	21	4			
UD					
No	111	45	0.323	0.026	-0.16~-0.056
Yes	5	0			
US					
No	108	42	1.0	0.081	-0.15~0.15
Yes	8	3			
BU					
No	114	45	1.0	0.02	-0.118~-0.044
Yes	2	0			

CES = continuous eversion suture; **CIS** = continuous inversion subepithelial; **UF** = cutaneous fistula; **UD** = urethral diverticulum; **US** = urethral stricture and **BU** = breakdown of urethral repair

the transverse preputial island flap (3, 9). Previous studies only mentioned that a well-vascularized neourethra and preputial flaps used for repair were exceptionally important for a successful outcome (10), but neglected how to improve intrinsic element of neourethra. We derived CIS from gastrointestinal anastomosis and hypospadias TIP technique which was reported to be easier to heal than other techniques (6, 11). In this study, we described the minimal modified repair of CIS with tubularized neourethra and compared it with CES.

UF can occur inside the neourethra or at its junction to the native urethra in TPIFU. There were various causes of failure, such as overlapping sutures, distal obstruction, ischemia tissue and single-layer coverage (12). Snodgrass reported that subepithelial urethroplasty would obviously decrease UF complication after proximal TIP, but he did not explain the reason (6). For the TPIFU, the comparison between CES and CIS had not been reported before. In our study, we adopted the CIS technique in neourethra and compared them with CES. The success rate of CES group was 69.8%, and CIS 84.4%. In spite of wide discrepancy in the patient's number of the two groups (116: 45), there were no statistical differences among perioperative variables. It demonstrated that the comparison of two group's postoperative complications was feasible and could not be influenced by these variables. By comparing the two groups, we found that the overall success rate and the incidences of the four complications had no statistical difference.

How to explain this pathophysiology? The answer should be seek for in wound healing process. Wounds normally heal in an orderly and efficient manner characterized by overlapping phases that include inflammation, epithelialization, fibroplasia, and maturation (13). The surface of the incision abutted closer in the CIS, while the epithelium abutted closer in the CES. The basal cell proliferation and epithelial cell migration occurring in the sutured margin might be slower within the latter suture. After being anastomosed with the native urethra and glans, the neourethra would touch the anastomosing surface to the cavernosa ventrally. The external anastomosing surface was much smoother with CIS as shown in Figure-2. So, they could abut together more tightly. As described above, it seemed like that continuous inversion subepithelial suture was easier to heal. But the UF and BU incidences had no difference between the two groups, it might be accounted for the subtle differences of techniques changing the process of establishing prime and side branches vascularization.

There were various risk factors leading to UD and US, such as ischemia and the appearance of neourethra (14). The neourethra's medial surface was rough with inversion incision as we all know and it might affect the results. But there were still no statistically significant differences between the two groups. It might be accounted for long time of catheterization (2~6 weeks). Someone reported that long time will lead to ischemia and infection (15), but others stated that a stent did not affect postoperative recovery (1). In our research, we did find obvious side effects, and the total success rate was acceptable (73.9%) as reported by other studies (6, 14).

The maneuvers of CES and CIS had no significantly different effect on the complications rates in TPIFU. Thus, CES and CIS could be randomly adopted in TPIFU as a personal preference.

Our study has some limitations: it had been reported that the vascular branch in the preputial island flap was associated with results of hypospadias repair (13). It's a flaw that we did not research it in our article. We did not practice routine uroflowmetry in the research. Besides, limited number of patients and a relatively short follow-up period to observe the outcomes and complications were also limitations.

FUNDING

This study was funded by Beijing outstanding talent training scheme (2016000021469G200), the Beijing hospital authority key medical professional development plan "yangfan" (ZYLX201709) and the Beijing hospital authority "dengfeng" talent training plan (DFL20151102).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Springer A, Krois W, Horcher E. Trends in hypospadias surgery: results of a worldwide survey. Eur Urol. 2011;60:1184-9.
2. Huang Y, Xie H, Lv Y, Yu L, Sun L, Li X, et al. One-stage repair of proximal hypospadias with severe chordee by in situ tubularization of the transverse preputial island flap. J Pediatr Urol. 2017;13:296-299.
3. Seo S, Ochi T, Yazaki Y, Okawada M, Doi T, Miyano G, et al. Soft tissue interposition is effective for protecting the neourethra during hypospadias surgery and preventing postoperative urethrocutaneous fistula: a single surgeon's experience of 243 cases. Pediatr Surg Int. 2015;31:297-303.
4. Chen C, Yang TQ, Chen JB, Sun N, Zhang WP. The Effect of Staged Transverse Preputial Island Flap Urethroplasty for Proximal Hypospadias with Severe Chordee. J Urol. 2016;196:1536-1540.
5. Liang WQ, Qiu YH, Ji CY, Chen YH, Zhang JQ, Yao YY, et al. A comparative study of surgical outcomes using a Colorado microdissection needle versus standard-size needle electrocautery in one-stage hypospadias repair using a transverse preputial island flap. Minerva Pediatr. 2018;70:27-34.
6. Snodgrass W, Bush N. TIP hypospadias repair: A pediatric urology indicator operation. J Pediatr Urol. 2016;12:11-8.
7. Duckett JW Jr. Transverse preputial island flap technique for repair of severe hypospadias. Urol Clin North Am. 1980;7:423-30.
8. Zheng DC, Wang H, Lu MJ, Chen Q, Chen YB, Ren XM, et al. A comparative study of the use of a transverse preputial island flap (the Duckett technique) to treat primary and secondary hypospadias in older Chinese patients with severe chordee. World J Urol. 2013;31:965-9.
9. Chua ME, Gnech M, Ming JM, Silangcruz JM, Sanger S, Lopes RI, et al. Preoperative hormonal stimulation effect on hypospadias repair complications: Meta-analysis of observational versus randomized controlled studies. J Pediatr Urol. 2017;13:470-480.
10. Han W, Zhang W, Sun N. Risk factors for failed urethrocutaneous fistula repair after transverse preputial island flap urethroplasty in pediatric hypospadias. Int Urol Nephrol. 2018;50:191-195.
11. Phitayakorn R, Delaney CP, Reynolds HL, Champagne BJ, Heriot AG, Neary P, et al. Standardized algorithms for management of anastomotic leaks and related abdominal and pelvic abscesses after colorectal surgery. World J Surg. 2008;32:1147-56.
12. Fahmy O, Khairul-Asri MG, Schwentner C, Schubert T, Stenzl A, Zahran MH, et al. Algorithm for Optimal Urethral Coverage in Hypospadias and Fistula Repair: A Systematic Review. Eur Urol. 2016;70:293-8.
13. Diegelmann RF, Evans MC. Wound healing: an overview of acute, fibrotic and delayed healing. Front Biosci. 2004;9:283-9.
14. Huang LQ, Guo YF, Ge Z, Lu RG, Deng YJ, Ma G, et al. A new modification of the Duckett technique for one-stage repairing urethral plate transected hypospadias: Another option for severe hypospadias? Int Urol Nephrol. 2017;49:2091-2097.
15. Lumen N, Hoebeke P, Willemsen P, De Troyer B, Pieters R, Oosterlinck W. Etiology of urethral stricture disease in the 21st century. J Urol. 2009;182:983-7.

Correspondence address:
Yanfang Yang, MD
40 North Road, 27 District University,
Zhengzhou, 450052, China
Telephone: +86 71 6665-8007
E-mail: wei_ping_zhang@126.com

ORIGINAL ARTICLE

Vol. 46 (5): 778-785, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0503

Retrograde pyelography before radical nephroureterectomy for upper tract urothelial carcinoma is associated with intravesical tumor recurrence

Young Hwii Ko [1], Phil Hyun Song [1], Taeyong Park [2], Jae Young Choi [1]

[1] Department of Urology, College of Medicine, Yeungnam University, Daegu, Republic of Korea; [2] Department of Urology, Pusan Paik Hospital, Inje University, Busan, Republic of Korea

ABSTRACT

Purpose: To investigate the association between preoperative retrograde pyelography (RGP), conducted to evaluate upper tract urothelial carcinoma (UTUC), and intravesical recurrence (IVR) after radical nephroureterectomy (RNU).

Materials and Methods: Of 114 patients that underwent RNU, 72 patients without preoperative ureteroscopy and a history of bladder tumor were selectively enrolled. Variables associated with IVR were identified.

Results: RGP was performed at a mean duration of 24.9 days prior to RNU in 41 (56.1%) of study subjects. During the mean follow-up period of 64.5 months, IVRs were identified in 32 (44.4%) patients at 22.3±18.8 (mean±SD) months after RNU. Despite similar tumor characteristics in the RGP and non-RGP groups, the incidence of IVR was considerably higher in the RGP group (63.4%) than in the non-RGP group (19.4%, p <0.001). The following variables differed significantly between the IVR and non-IVR groups: age (64.6±8.51 vs. 59.6±9.65 years), tumor location (lower or upper; 53.1% vs. 20%), tumor invasiveness (> pT2; 53.1% vs. 17.5%), preoperative hemoglobin (12.8±1.36 vs. 13.9±1.65), preoperative creatinine (1.29±0.32 vs. 1.11±0.22), and preoperative RGP (81.3% vs. 37.5%), respectively. Multivariate Cox regression model showed that tumor location (p=0.020, HR=2.742), preoperative creatinine level (p=0.004, HR=6.351), and preoperative RGP (p=0.045, HR=3.134) independently predicted IVR.

Conclusion: Given the limitations of retrospective single-center series, performance of RGP before RNU was shown to have a negative effect on IVR after surgery.

ARTICLE INFO

Young Hwii Ko
http://orcid.org/0000-0002-9150-4292

Keywords:
Urography; Nephroureterectomy; Neoplasms

Int Braz J Urol. 2020; 46: 778-85

Submitted for publication:
August 07, 2019

Accepted after revision:
January 26, 2020

Published as Ahead of Print:
April 10, 2020

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) accounts for 5-10% of urothelial neoplasms and 10% of renal tumors (1). Radical nephroureterectomy (RNU) with bladder cuffing is the established 'gold standard' for the management of UTUC (2). However, intravesical recurrence (IVR) occurs after 22-47% of procedures (3-5). Two dominant theories have been proposed to explain the mechanism of IVR: monoclonal and oligoclonal spread. According to the former hypothesis, IVR produces abnormal cell spread to the bladder before RNU or may increase the ability of locally budding tumors to release cancer cells into the urinary tract (6). On the other hand, the latter

hypothesis involves carcinogenic exposure of the entire urothelial layer leading to independent multifocal tumor development within the urinary tract (7).

Increased rates of IVR after diagnostic ureterorenoscopy (URS) and prior to RNU have been reported by several authors, and a recent meta-analysis demonstrated an obvious association between the two (8, 9). These observations provide evidence that supports the monoclonal-spreading theory because URS with/without biopsy facilitates detachment and migration of abnormal urothelial cells into the lower urinary tract. For this study, we hypothesized that if URS truly increases the risk of IVR, then retrograde pyelography (RGP), which is a less invasive alternative to URS, might also give rise to IVR. In an attempt to identify the mechanism responsible, we investigated the effect of preoperative RGP on IVR after RNU among patients that did not receive preoperative URS.

MATERIALS AND METHODS

Patient collection and RGP procedure

Of 114 patients that underwent RNU for UTUC from January 2004 to June 2013 at our institution, 72 patients that did not undergo preoperative URS and had no history of bladder cancer were selectively enrolled, after approval obtained from the local institutional review board (YUMC 2017-12-018-001). Because our institution has no universal policy regarding the use of RGP as a radiologic tool to identify the presence of UTUC, the durations between RGP and RNU differed. However, RGP was performed as a separate procedure before RNU in all cases. RGP was performed by a urologic resident under local anesthesia using a 6Fr size ureteral catheter (open-end ureteral catheter, Cook Medical, Bloomington, IN, USA), which was inserted approximately 5-10cm from the ipsilateral ureteral orifice with cystoscope and fluoroscope guidance. At the time of RGP, the absence of suspicious bladder lesions was confirmed by cystoscopy. All 72 study subjects underwent computed tomography (CT) as a baseline diagnostic modality. At the time of RNU, bladder cuffing was performed by applying the open method, regardless of nephrectomy approaches (open or laparoscopic), using a modified Gibson incision.

Clinicopathologic variables and follow-up after RNU

The histologic characteristics of UTUC were based on examinations of specimens obtained during RNU and included stage, grade, and lympho-vascular invasion (LVI). Tumor locations were determined by CT and RGP and dichotomized as upper (upper ureter and renal pelvis) or lower. Intra-ureteral tumor size was defined as the maximal tumor dimension within the urinary tract as determined by examining sagittal or coronal CT or RGP images. Hemoglobin and creatinine levels before RNU were also collected, due to their reported associations with IVR (6, 9, 10).

After RNU, patients were followed-up by four urological specialists who performed CT, cystoscopy, and urine cytology examinations on a 6- to 12-month basis for five years. Because of limited approval regarding the preventive use of intravesical chemo- or immunotherapy for UTUC in our country, no immediate intravesical therapy was implemented after RNU. When IVR was identified during follow-up surveillance, we recorded the duration between RNU and IVR.

Statistical analysis

The endpoint of this study was the first IVR of urothelial carcinoma (UC) after RNU, which was defined as the first histologically confirmed bladder UC, regardless of tumor characteristics and number. The significances of differences between patients with or without IVR were compared by applying t and chi-squared tests, and associations between variables were identified using bivariate correlation analysis. Given the influence of time after RNU on IVR, the impacts of preoperative RGP and other clinicopathological factors on IVR were analyzed using a multivariate Cox proportional hazard model. The log-rank test was used for the comparison of each variable in a Kaplan-Meier model, and distribution normality was checked using the Kolmogorov-Smirnov test. The analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Two-

-sided tests were used and the significance level was set at 5%.

RESULTS

Characteristics of the study subjects

Forty-one (56.1%) of the 72 study subjects underwent RGP to determine the presence of UTUC before RNU. Patient characteristics are summarized in Table-1. The 41 patients in the RGP group were significantly older than the patients in the non-RGP group (mean±SD; 64.5±8.9 vs. 58.3±9.0 years, p=0.005), but the results for the other variables (sex, LVI, preoperative creatinine, and hemoglobin levels, total operative time, and tumor size, location, stage, and grade) were similar in these two groups. Despite a shorter mean follow-up period (31.3±23.1 vs. 48.3±18.6 months, p=0.001), bladder tumor recurrence rate was markedly higher in the RGP group (63.4% [26/41] vs. 19.4% [6/31]; p <0.001). The mean time between RGP and RNU in the RGP group was 24.9 days.

Variables associated with IVR

During the mean follow-up period of 64.5 months, 32 (44.4%) of the 72 study subjects developed IVR at a mean duration of 22.3±18.8 months after RNU. Table-2 summarizes differences detected between the IVR (n=32) and non-IVR (n=40) groups. Patients in the IVR group were significantly older (64.6±8.51 vs. 59.6±9.65 years; p=0.005). IVR group had a higher percentage of patients with lower tumor location (53.1% vs. 20%, p=0.032) and invasive tumors (> pT2; 53.1% vs. 17.5%, p=0.011). They had a lower preoperative hemoglobin level (12.8±1.36 vs. 13.9±1.65, p=0.004), a higher preoperative creatinine level (1.29±0.318 vs. 1.11±0.221, p=0.009), and a higher percentage of patients underwent preoperative RGP (81.3% vs. 37.5%. p <001). However, the durations between RGP and RNU, which were normally distributed (two-tailed asymptomatic significance=0.531), were similar in these two groups (22.8±17.9 vs. 28.6±23.1 days, p=0.411). Tumor sizes, which were also normally distributed (mean 34.9mm; two-tailed asymptomatic significance=0.162), were also similar in the two groups (34.1±14.9 vs. 35.6±17.5mm, p=0.715).

ultivariate analysis and the association between preoperative RGP and IVR

Multivariate Cox proportional hazard model analysis showed that tumor location (p=0.020, hazard ratio [HR]=2.742, 95% confidence index [CI]: 1.169-6.430), preoperative creatinine level (p=0.004, HR=6.351, 95% CI: 1.587-12.361), and receipt of preoperative RGP (p=0.045, HR=3.134, 95% CI: 1.027-9.560) were individually associated with IVR. Moreover, Kaplan-Meier analysis showed that preoperative RGP was significantly associated with IVR (p <0.001, Figure-1).

DISCUSSION

The pathogenesis of IVR following RNU for UTUC remains unclear. Because IVR recurrence rates after RNU have been consistently reported to be clinically significant, several authors have sought to determine whether patient-, tumor-, and/or treatment-specific parameters are associated with recurrence. Systemic reviews on RNU indicate previous bladder cancer, concomitant chronic kidney disease, tumor location on the ureter, the presence of LVI, tumor multiplicity, invasive pT stage, and positive surgical margins are associated with IVR in this patient population (6, 9). In a recently published meta-analysis, it was concluded that, in addition to these variables, receipt of URS before RNU elevated the risk of IVR (9), despite other evidence to the contrary (8, 11).

The present study is the first to report the effects of RGP before RNU on IVR, for patients that have not undergone preoperative URS. Advances in endoscopic equipment have made URS more accessible and have enabled its use in exploring the entire upper urinary tract. As a result, URS is rapidly replacing RGP for the identification of UTUC (12). Thus, our objective was not to evaluate the risk of IVR posed by preoperative RGP, but rather to investigate the mechanism responsible for IVR in this setting.

Several interesting observations were made during the present study. First, we detected a significant association between preoperative RGP and IVR following RNU. Importantly, the IVR rate was significantly higher in the RGP group than in the non-RGP group, and multivariate analysis

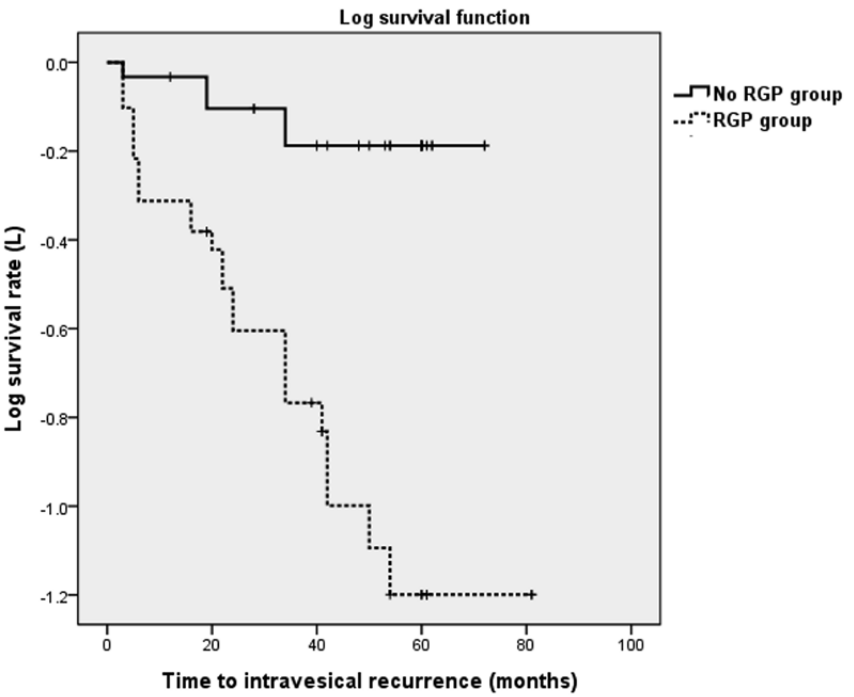
Table 1 - Characteristics of patients in the retrograde pyelography (RGP) and non-RGP groups.

		Total (N=72)			RGP (N=41)			No RGP (N=31)			P-value
		N	%	Mean (±SD)	N	%	Mean (±SD)	N	%	Mean (±SD)	
Gender	Female	14	19.4%		11	26.8%		3	9.7%		0.069
	Male	58	80.6%		30	73.2%		28	90.3%		
Age (years)				**61.81 (±9.44)**			**64.49 (±8.98)**			**58.26 (±8.99)**	**0.005**
	< 65	41	56.9%		16	39.0%		25	80.6%		<0.000
	≥ 65	31	43.1%		25	61.0%		6	19.4%		
Length of tumor (mm)				**34.92 (±16.3)**			**32.54 (±15.5)**			**38.06 (±17.0)**	**0.161**
	< 35	35	48.6%		25	61.0%		10	32.3%		0.016
	≥ 35	37	51.4%		16	39.0%		21	67.7%		
Location of tumor	Upper	47	65.3%		23	56.1%		24	77.4%		0.062
	Lower	25	34.7%		18	43.9%		7	22.6%		
Multiplicity of tumor	Single	67	93.1%		40	97.6%		27	87.1%		0.158
	Multiple	5	6.9%		1	2.4%		4	12.9%		
T stage	T1	48	66.7%		24	58.5%		24	77.4%		0.113
	T2	12	16.7%		7	17.1%		5	16.1%		
	T3	12	16.7%		10	24.4%		2	6.5%		
	Non-invasive	48	66.7%		24	58.5%		24	77.4%		0.092
	Invasive (≥pT2)	24	33.3%		17	41.5%		7	22.6%		
Tumor grade	low	24	33.3%		13	31.7%		11	35.5%		0.736
	high	48	66.7%		28	68.3%		20	64.5%		
Lymphvascular invasion	No invasion	64	88.9%		36	87.8%		28	90.3%		0.736
	With invasion	8	11.1%		5	12.2%		3	9.7%		
Preoperative hemoglobin (g/dL)				**13.37 (±1.61)**			**13.17 (±1.59)**			**13.65 (±1.61)**	**0.221**
	≥ 10	70	97.2%		39	95.1%		31	100%		0.212
	< 10	2	2.8%		2	4.9%		0	-		
Preoperative creatinine (mg/dL)				**1.19 (±.281)**			**1.22 (±.320)**			**1.14(±.217)**	**0.233**
	< 1.5	57	79.2%		29	70.7%		28	90.3%		0.043
	≥ 1.5	15	20.8%		12	29.3%		3	9.7%		
Total operative time (minutes)				**384.65 (±79.5)**			**368.78 (±95.7)**			**405.65 (±44.1)**	**0.051**
Follow up period (months)				**38.58 (±22.8)**			**31.27 (±23.1)**			**48.26 (±18.6)**	**0.001**
Intravesical recur during follow up	No recur	40	55.6%		15	36.6%		25	80.6%		<0.000
	Bladder recur	32	44.4%		26	63.4%		6	19.4%		
Time from RGP to RNU (days)				**24.93 (±19.9)**			**24.93 (±19.9)**			.	
	< 7	13	31.7%		13	31.7%		-			
	≥ 7	28	68.3%		28	68.3%		-			

Table 2 - Characteristics of patients in the intravesical recurrence (IVR) and non-IVR groups.

		Total (N=72)			IVR (N=32)			No IVR (N=40)			P-value
		N	%	Mean (±SD)	N	%	Mean (±SD)	N	%	Mean (±SD)	
Gender	Female	14	19.4%		10	31.3%		4	10%		0.021
	Male	58	80.6%		22	68.8%		36	90%		
Age (years)				**61.81 (±9.44)**			**64.63 (±8.51)**			**59.55 (±9.65)**	**0.005**
	< 65	41	56.9%		13	40.6%		28	70%		0.012
	≥ 65	31	43.1%		19	59.4%		12	30%		
Length of tumor (mm)				**34.92 (±16.3)**			**34.13 (±14.86)**			**35.55 (±17.49)**	**0.715**
	< 35	35	48.6%		19	59.4%		16	40%		0.102
	≥ 35	37	51.4%		13	40.6%		24	60%		
Location of tumor	Upper	47	65.3%		15	46.9%		32	80%		0.032
	Lower	25	34.7%		17	53.1%		8	20%		
Multiplicity of tumor	Single	67	93.1%		32	100%		35	87.5%		0.061
	Multiple	5	6.9%		0	-		5	12.5%		
T stage	T1	48	66.7%		15	46.9%		33	82.5%		0.061
	T2	12	16.7%		8	25.0%		4	10.0%		
	T3	12	16.7%		9	28.1%		3	7.5%		
	Non-invasive	48	66.7%		15	46.9%		33	82.5%		0.011
	Invasive (≥pT2)	24	33.3%		17	53.1%		7	17.5%		
Tumor grade	low	24	33.3%		7	21.9%		17	42.5%		0.065
	high	48	66.7%		25	78.1%		23	57.5%		
Lymphvascular invasion	No invasion	64	88.9%		28	87.5%		36	90%		0.737
	With invasion	8	11.1%		4	12.5%		4	10%		
Preoperative hemoglobin (g/dL)				**13.37 (±1.61)**			**12.79 (±1.36)**			**13.85 (±1.65)**	**0.004**
	≥ 10	70	97.2%		30	93.8%		40	100%		0.109
	< 10	2	2.8%		2	6.3%		0	-		
Preoperative creatinine (mg/dL)				**1.19 (±.281)**			**1.29 (±.318)**			**1.11 (±.221)**	**0.009**
	< 1.5	57	79.2%		21	65.6%		36	90%		0.011
	≥ 1.5	15	20.8%		11	34.4%		4	10%		
Total operative time (minutes)				384.65 (±79.5)			372.03 (±88.2)			394.75 (±71.3)	0.243
Follow up period (months)				38.58 (±22.8)			22.34 (±18.83)			51.58 (±16.6)	<.000
RGP before RNU	RGP	41	56.9%		26	81.3%		15	37.5%		<.000
	No RGP	31	43.1%		6	18.8%		25	62.5%		
Time from RGP to RNU (days)				**24.93 (±19.9)**			**22.81 (±17.93)**			**28.60 (±23.1)**	**0.411**
	< 7	13	31.7%		10	38.5%		3	20%		0.221
	≥ 7	28	68.3%		16	61.5%		12	80%		

Figure 1 - Kaplan-Meier curve for intravesical tumor recurrence after nephroureterectomy with or without preoperative RGP (p <0.001 from the log-rank test).



adjusted for intergroup differences showed preoperative RGP, along with tumor location and preoperative creatinine level, independently predicted IVR. We believe this relationship supports the monoclonal theory of UTUC spread to the bladder, despite the fact that the retrospective design of this study prevented assessment of causality.

Second, we included intra-ureteral (or intra-pelvic) tumor size as a potential variable, because we considered a larger ureteral lesion would probably increase the risk of bladder exposure by facilitating tumor detachment during RGP. Two previous series have reported the effect of tumor size on IVR, but neither provided a clear definition of size or of the measuring method used. Ku et al. enrolled 181 patients that underwent RNU and divided them by tumor size using an approximate cut-off of 30mm but detected no association with IVR when applying Cox regression analysis (Odds ratio=1.268, p=0.435) (13). Zou et al. studied 122 patients that underwent RNU with a mean tumor size of 29.9mm (range: 2-120mm), which was similar to that observed in the present study (mean=34.9mm; range: 10-40mm). However, in this previous study (14), multivariate analysis failed to detect an effect of tumor size on IVR, which concurs with our findings and those of a recent meta-analysis (6). These observations imply that IVR is a complicated phenomenon with a mixed pathogenesis. In the present study, we observed that tumor location, rather than tumor size, had a significant influence on IVR.

Third, despite a strong relationship with preoperative RGP, the length of time between RGP and RNU was not observed to influence IVR. Originally, we considered the exposure duration for normal bladder urothelium to detach UTUC cells would be associated with IVR. However, the periods between RGP and RNU were similar in the IVR and non-IVR groups. Furthermore, when the RGP group was dichotomized using time from RGP to RNU cut-off periods of 7 days (22%), 10 days (31.7%), or the median period of 23 days (51.2%), no significant differences in IVR rates were observed (data not shown). Given that 73.2% of RNU procedures were performed within one month (97.6% within two months) of RGP, this finding implies an RGP to RNU time of longer than one

month is required to influence IVR. In addition, given that a single session of URS plus RNU was not associated with an increase in IVR (15, 16), it would appear that members of the RGP group with almost a month interval had similar risks of developing IVR because all RGP procedures were performed separately.

We are aware that the present study has several limitations. First, because the contemporary diagnosis of UTUC was conducted based predominantly on CT and URS results rather than on RGP findings, we had to enroll patients over almost a decade, which raised issues regarding the effects of possible changes in UTUC management. For example, adjuvant chemotherapy on >pT3 disease was only conducted in 5 of 12 subjects, which may have biased IVR outcomes. In addition, the prolonged enrollment period, unfortunately, caused age to be significantly different in the RGP and non-RGP groups (Table-1). Second, postoperative follow-up after RNU was performed by four urological specialists; in addition, surgical volumes differed and indications for RGP were not standardized. Third, the study was performed using retrospective data collected at a single center, which cautions that the study outcomes should be interpreted with care. Fourth, the primary endpoint, IVR, was not determined by a single modality, but rather was determined by radiologic and cystoscopic evaluation regardless of bladder tumor status. Further study will no doubt shed additional light on the mechanisms associated with IVR and the effect of intra-ureteral instrumentation.

CONCLUSIONS

Given the limitations of a retrospective, single-center series, RGP before RNU was shown to have a negative effect on IVR after surgery, regardless of the length of time between RGP and RNU. We suggest that the results provide evidence supporting the theory that monoclonal tumor cell spread underlies the pathogenesis of IVR.

ACKNOWLEDGMENT

This work was supported by a Yeungnam University Research Grant (2018).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62:10-29.
2. Redrow GP, Matin SF. Upper tract urothelial carcinoma: epidemiology, high risk populations and detection. Minerva Urol Nefrol. 2016;68:350-8.
3. Wu WJ, Ke HL, Yang YH, Li CC, Chou YH, Huang CH. Should patients with primary upper urinary tract cancer receive prophylactic intravesical chemotherapy after nephroureterectomy? J Urol. 2010;183:56-61.
4. Xylinas E, Colin P, Audenet F, Phe V, Cormier L, Cussenot O, et al. Intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinomas: predictors and impact on subsequent oncological outcomes from a national multicenter study. World J Urol. 2013;31:61-8.
5. Zigeuner RE, Hutterer G, Chromecki T, Rehak P, Langner C. Bladder tumour development after urothelial carcinoma of the upper urinary tract is related to primary tumour location. BJU Int. 2006;98:1181-6.
6. Seisen T, Granger B, Colin P, Léon P, Utard G, Renard-Penna R, et al. A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol. 2015;67:1122-1133.
7. Yamany T, van Batavia J, Ahn J, Shapiro E, Gupta M. Ureterorenoscopy for upper tract urothelial carcinoma: how often are we missing lesions? Urology. 2015;85:311-5.
8. Tan P, Xie N, Yang L, Liu L, Tang Z, Wei Q. Diagnostic Ureteroscopy Prior to Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma Increased the Risk of Intravesical Recurrence. Urol Int. 2018;100:92-99.
9. Guo RQ, Hong P, Xiong GY, Zhang L, Fang D, Li XS, et al. Impact of ureteroscopy before radical nephroureterectomy for upper tract urothelial carcinomas on oncological outcomes: a meta-analysis. BJU Int. 2018;121:184-193.
10. Liu Y, Lu J, Hong K, Huang Y, Ma L. Independent prognostic factors for initial intravesical recurrence after laparoscopic nephroureterectomy for upper urinary tract urothelial carcinoma. Urol Oncol. 2014;32:146-52.
11. Ishikawa S, Abe T, Shinohara N, Harabayashi T, Sazawa A, Maruyama S, et al. Impact of diagnostic ureteroscopy on intravesical recurrence and survival in patients with urothelial carcinoma of the upper urinary tract. J Urol. 2010;184:883-7.

12. Takao A, Saika T, Uehara S, Monden K, Abarzua F, Nasu Y, et al. Indications for ureteropyeloscopy based on radiographic findings and urine cytology in detection of upper urinary tract carcinoma. Jpn J Clin Oncol. 2010;40:1087-91.
13. Ku JH, Choi WS, Kwak C, Kim HH. Bladder cancer after nephroureterectomy in patients with urothelial carcinoma of the upper urinary tract. Urol Oncol. 2011;29:383-7.
14. Zou L, Zhang L, Zhang H, Jiang H, Ding Q. Comparison of post-operative intravesical recurrence and oncological outcomes after open versus laparoscopic nephroureterectomy for upper urinary tract urothelial carcinoma. World J Urol. 2014;32:565-70.
15. Lee JK, Kim KB, Park YH, Oh JJ, Lee S, Jeong CW, et al. Correlation Between the Timing of Diagnostic Ureteroscopy and Intravesical Recurrence in Upper Tract Urothelial Cancer. Clin Genitourin Cancer. 2016;14:e37-41.
16. Sung HH, Jeon HG, Han DH, Jeong BC, Seo SI, Lee HM, et al. Diagnostic Ureterorenoscopy Is Associated with Increased Intravesical Recurrence following Radical Nephroureterectomy in Upper Tract Urothelial Carcinoma. PLoS One. 2015;10:e0139976.

Correspondence address:
Jae Young Choi, MD
Department of Urology,
College of Medicine, Yeungnam University
317-1 Daemyung-dong, Nam-gu,
Daegu 705-035, Republic of Korea
Telephone: + 82 536 203-695
E-mail: urokyh@naver.com

ORIGINAL ARTICLE

Vol. 46 (5): 786-793, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0521

Novel semirigid ureterorenoscope with irrigation and vacuum suction system: introduction and initial experience for management of upper urinary calculi

Shu Gan [1], Zhenlang Guo [1], Qianming Zou [1], Chiming Gu [1], Songtao Xiang [1], Siyi Li [1], Zhangqun Ye [2], Shusheng Wang [1]

[1] *Department of Urology, The Second Affiliate Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China;* [2] *Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

ABSTRACT

Objective: This study aims to design a novel semirigid ureterorenoscope with irrigation and vacuum suction system and a modified ureteral access sheath (UAS) named Sotn ureterorenoscope® (Sotn=ShuoTong Medical Company) to overcome the deficiencies of the current procedure and to improve the efficiency and safety of using Sotn ureterorenoscope® for treatment of upper urinary calculi.

Materials and Methods: Fifty-eight patients, comprising 31 males and 27 females, were evaluated. The medical records of 58 patients with upper urinary calculi treated with Sotn ureterorenoscope® from March 2015 to June 2017 were retrospectively reviewed at the Second Affiliate Hospital of Guangzhou University of Chinese Medicine in China. The primary outcome was stone-free rate (SFR) assessed by computed tomography on the 1st day and one month after treatment. The secondary outcome was postoperative complication rate.

Results: The mean and SD of operative duration was 48.5 (10.4) min, and the mean and SD of stone size was 15.6 (5.6) mm. The primary overall SFR was 89.7% (52/58) and 100% at 1 month follow-up. Complication, which was Clavien I (minor fever managed by antipyretic therapy), was detected in 1.7% (1/58) of the patients.

Conclusions: Sotn ureterorenoscope® is technically feasible, efficacious and safe for treatment of upper urinary calculi because of its advantages of high SFR and low complication rates.

ARTICLE INFO

Shusheng Wang
http://orcid.org/0000-0002-4567-3407

Keywords:
Urinary Calculi; Vacuum; Urolithiasis

Int Braz J Urol. 2020; 46: 786-93

Submitted for publication:
August 13, 2019

Accepted after revision:
November 01, 2019

Published as Ahead of Print:
April 10, 2020

INTRODUCTION

Urolithiasis has recently attracted considerable attention worldwide because of its increasing morbidity and recurrence rates, this disease seriously affects the quality of life of afflicted individuals and increase the economic burden on the society globally (1, 2). As a low-risk procedure with a high retreatment rate (18% to 67%), extracorporeal shock wave lithotripsy (ESWL) often leads to persistent residual stones (3, 4). When surgery is indicated for ureteral stones, ureteroscopic holmium-YAG laser lithotripsy is currently the mainstay therapy. However, the two major drawbacks of this procedure are stone retropulsion and stone fragment management in the ureter (5). Fle-

xible ureteroscopy can minimize risks associated with bleeding and visceral injury, but the non-ideal pelvicaliceal anatomy and poor durability of flexible ureteroscopy may affect its success rate and applications (6, 7).

Percutaneous nephrolithotomy (PCNL) can be performed safely and effectively to achieve high stone-free rate (SFR) and allows for short treatment period in most patients, despite its well-known hazardous and serious complications. Most of these complications are related to tract formation and size (8, 9).

Here, we designed a novel semirigid ureterorenoscope with irrigation and vacuum suction system and its modified ureteral access sheath (UAS) named Sotn ureterorenoscope® (Sotn=ShuoTong Medical Company). This study aimed to assess the efficiency and safety of using Sotn ureterorenoscope for treatment of upper urinary calculi.

MATERIALS AND MEASURES

Patients and methods

Our study was performed in strict accordance with the requirements of the Ethics Committee of the Second Affiliate Hospital of Guangzhou University of Chinese Medicine and under their supervision. Patients were informed that they would undergo a new technique. The risks and benefits were explained, and written informed consent was obtained from each participant or their legal guardian. Modified sheaths and specimen collection bottles were provided for free.

The inclusion criteria were as follows: (1) patients aged >18 years, (2) presence of radiopaque stones, (3) identification of upper urinary calculi and lower renal pole (upper ureteral stone, renal pelvis stone and upper and middle renal calyx stones) ≤3 cm in diameter on abdominal non-contrast computed tomography (CT) and (4) male and female patients. Patients with anatomically abnormal urinary systems (i.e. ureteral stenosis), coagulation abnormalities and uncontrolled infection of the urinary system as well as those who were pregnant were excluded from the study. SFR was evaluated according to the abdominal CT scan on the 1st day and 1st month after Sotn ureterorenoscopy. Moreover, the primary SFR was defined as the detection of residual fragments <2mm in diameter on abdominal non-contrast CT. Complications within 1 month postoperatively were assessed and classified according to the modified Clavien-Dindo classification system. Postoperative temperature of >38°C was defined as fever.

Novel surgical device

The detailed description of Sotn ureterorenoscope® is presented on the following website: http://sotnmedical.com. The new surgical equipment consists of a standard ureteroscope (length of 45cm and outer diameter of 7.5 (tip)/11.3F (shaft), Patent no. ZL201110030512.9), a modified UAS (metal material, tapered tip, no hydrophilic coating, length of 40cm and outer diameter of 11.6 or 12.9F; Figure-1; Patent no. ZL201430394938.7), mini-ureteroscope (length of 46cm and outer diameter of 4 (tip)/6F [shaft]; Figure-2; Patent no. ZL201120029461.3), an irrigation and vacuum suction system (Patent no. ZL201420607795.4), an adapter (Patent nos. ZL201430394936.8 and ZL201520891360.5) and Lumenis Holmium laser (maximum power, 100W, Figure-3).

Figure 1 - Standard ureteroscope and modified ureteral access sheath.

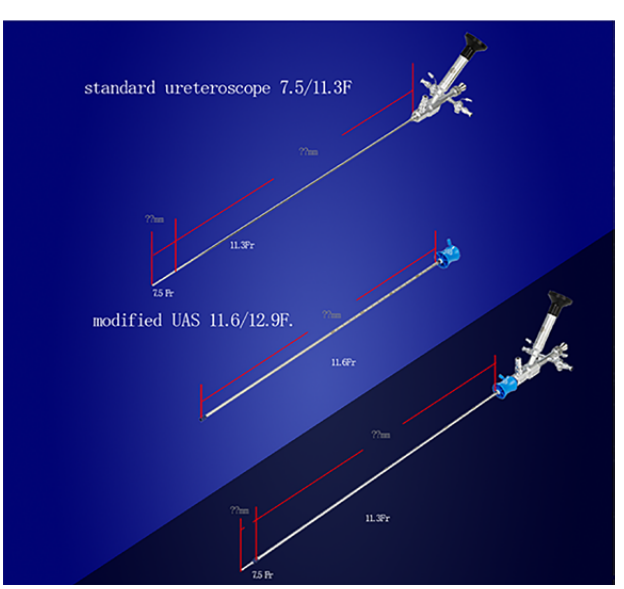


Figure 2 - Mini-ureteroscope.

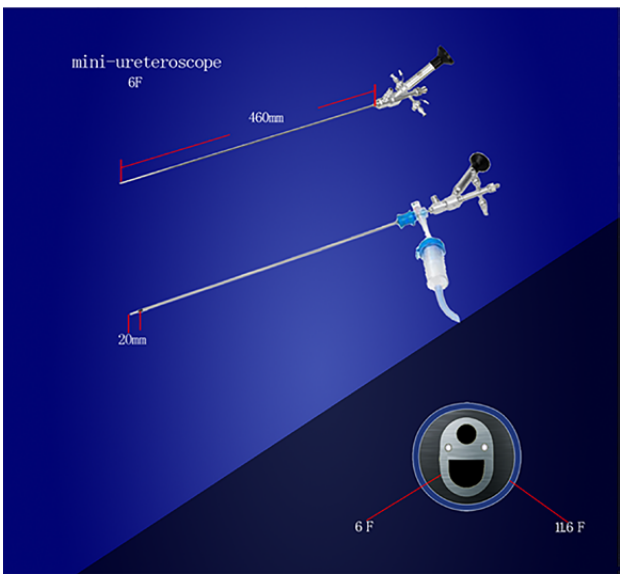
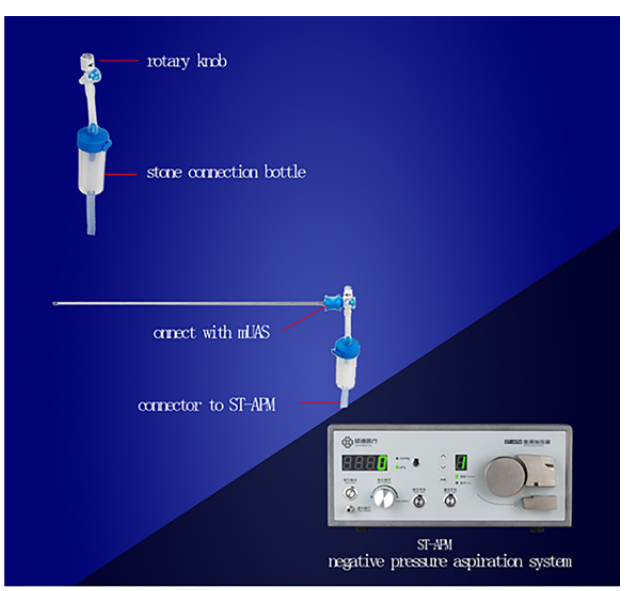


Figure 3 - Continuous negative pressure aspiration system and Lumenis Holmium laser (maximum power, 100W).



Surgical techniques

Patients were placed in lithotomy position, with head 30° lower and affected side 15° higher. Intratracheal intubation anaesthesia was applied in operations. The standard ureteroscope connected to the modified UAS was inserted into the upper ureter or renal pelvis guided by zebra guide wire under direct vision. The standard ureteroscope was disconnected and removed. The mini-ureteroscope was connected to the modified UAS through the adapter with stone collection bottle. The other side of the bottle was also connected to the irrigation and vacuum suction system. The 200μm laser fibre was inserted through the working channel of the mini-ureteroscope, and the stones were shredded into fragments. The laser power was set at 8-20W (0.4-1.0J, 20-40Hz). The perfusion flow speed was set in continuous mode and ranged from 60mL/min to 610mL/min. The laser was turned on before insertion of the mini-ureteroscope with the irrigation and vacuum suction system. Negative pressure was set from-25k Pa to -4kPa in continuous mode for suction fragments, and the pressure was reduced during the operation. The renal pelvis and visible calyx were checked, and X-ray was used to confirm the absence of residual stones in the lower renal calyx during the operation. The infusion pump was stopped, and the negative-pressure suction was used when no apparent stones were found. The mini-ureteroscope and the irrigation and vacuum suction system were removed and the modified UAS with the standard ureteroscope was used. The standard ureteroscope and the modified UAS were simultaneously removed under direct vision. A 4.7F Double-J ureter stent was placed in the patient at the end of the operation and removed 2-6 weeks postoperatively. The procedure of using Sotn ureterorenoscope® is shown in Figure-4, and the animated version is provided in the supplementary material (see link video).

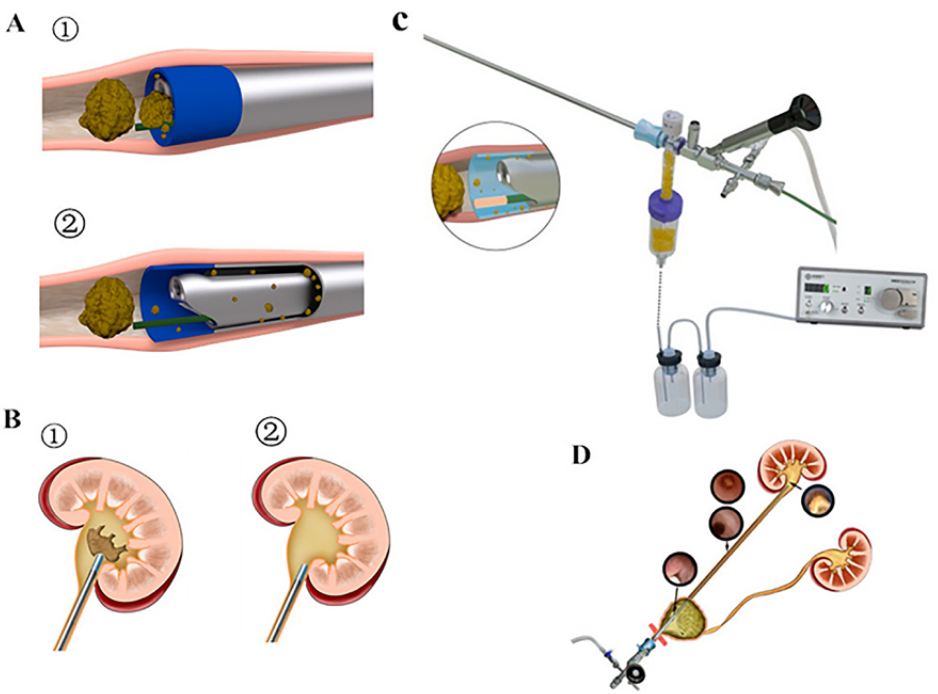
Statistical analysis

Statistical analysis was conducted using Stata/SE13.0. The amount data variables were described as median (interquartile range). Classification data were described as percentage. Continuous variables were assessed using Kruskal-Wallis tests for nonparametric data. Differences were considered statistically significant at $P < 0.05$ in all tests.

RESULTS

Fifty-eight patients, including 31 males and 27 females, were evaluated. The age of the

Figure 4 - Procedures of Sotn ureterorenoscopy. A - (①, ②) Scheme of stone dust removal by the suctioning system through interspace between the shaft of the console ureterorenoscope and modified UAS. B - (①, ②) Comparison of preoperative and postoperative conditions of renal stones. C - Sotn ureterorenoscopy. D - Surgery scheme.



patients ranged from 25 to 82 years, with average age of 53±12.6 years. The mean diameter of stone was 15.6±5.6mm. The mean and SD of stone volume was 1330±923mm^3. The detailed characteristics of the patients are shown in Table-1. Among the 58 patients, the intraoperative placement of the UAS in one patient (1.7%) failed in the first stage of surgery. A 4.7F Double-J ureter stent was then placed and kept for 2-6 weeks. Operative duration was 48.5±10.4min. The overall initial SFRs were also 89.7% (52/58) and 100% at 1 month follow--up. Complication, which was Clavien I (minor fever managed by antipyretic therapy), occurred in 1.7% (1/58) of the patients, and no transfusions were ne-

Table 1 - Demographics and stone characteristics of patients who underwent Sotn ureterorenoscopy.

Variable	Value
Number of patients	58
Failed UAS placement of Sotn ureterorenoscopy (n, %)	1 (1.7%)
Sotn ureterorenoscopy completed (n, %)	59
Male/female (n, %)	31 (53.4%)/27 (46.6%)
Mean (SD, range) stone size (cm)	1.56 (0.56, 0.6-3.2)
Number of stone site (n, %)	
Upper ureteral stone	30 (51.8%)
Middle renal calyx stone	11 (19%)
Renal pelvis stone	24 (41.4%)
Multiple (ureteric and renal stones)	9 (15.5%)

eded. The post-operative renal functions of patients were also normal. No ureteral pseudochannels, perforations, avulsions, ureteric stone street formations and perirenal hematomas were detected (Table-2).

DISCUSSION

Conventional option for treatment of renal stones with a maximum diameter of >20mm is open surgery or PCNL (10). PCNL is effective in treating renal stones but requires establishing channels through the renal parenchyma. Complications, including haemorrhage, infection and adjacent organ damage, were recorded when PCNL was utilized (11). Given the developments in natural endoscopic instruments and techniques, an increasing number of urological surgeons have chosen to treat renal stones by using natural channels. However, semirigid ureteroscope may be ineffective for treating upper large ureteral stones (12, 13). Flexible ureteroscope exhibits enhanced capability for treatment of all ureteral stones. Meanwhile, semirigid ureteroscope with size of <9F is a suitable device for distal ureteral calculi. When modern lithotripters are applied, approximately 90%-100% of ureteral stones can be fragmented (14). Furthermore, about 32% of patients may not be successfully treated because of mucosal oedema and ureteral stenosis. Flexible ureteroscope can be used to approach and fragmentise the located stones in such cases or stones that retropulse into the renal area (15, 16). Mursi et al. (13) reported that the SFR significantly decreased after the stones were treated with semirigid ureteroscope in the upper ureter. In a case report of 466 patients who underwent flexible ureteroscopies, 209 patients had renal stones with a maximum diameter of >20mm; the results showed that flexible ureteroscopy is safe and effective (17). In this regard, renal stones with a maximum diameter of >20mm can be safely treated using a natural channel flexible ureteroscope.

In our study, the final overall SFR was 89.7%, which was higher than that reported in a previous work on flexible ureteroscopy. A previous study comprising 316 consecutive patients who underwent flexible ureteroscopy reported an SFR of 70.5% (18). However, flexible ureteroscope with a suction system achieved primary SFR of 95.6% for patients with stone sizes ranging from 8mm to 35mm (19). This finding confirms the benefit of flexible ureteroscopy with our device. For placement of the ureter sheath, Mogilevkin et al. (20) reported that the ureter sheath cannot be used for 22% of patients in their primary surgery and should only be placed in their second surgery of flexible ureteroscopy. The ureteral wall and renal pelvis can be easily damaged because UAS is not placed by direct vision, which results in the perforation of the ureteral or pyeloneal mucosa and avulsion. Traxer et al. (21) discovered that up to 46.5% patients were injured in their ureter walls

Table 2 - Intraoperative and postoperative variables.

Variable	Value
Mean (SD, range) operative time (min)	48.5±10.4
Primary SFR (n/N, %)	89.7% (52/58)
Final SFR at 1 month (n/N, %)	100%
Required auxiliary procedure (n, %)	1.7% (1/58)
Significant complication (n, %)	1.7% (1/58)
Fever (>38.5°C)	1.7% (1/58)
Blood transfusion rate	0
Number of stone composition (n (%)	
Calcium oxalate stone	40 (68.97%)
Uric acid stone	5 (8.6%)
Calcium phosphate stone	13 (22.43%)

at different levels due to UAS. Finally, our study indicated that complication, which was Clavien I (minor fever managed by antipyretic therapy), occurred in 1.7% (1/58) of the patients, and no transfusions were needed. However, the intraoperative perfusion pressure during the surgery of flexible ureteroscopy was relatively high. The incidence rates of passive reflux, postoperative fever (10.7%) and sepsis (3.4%) were high (22).

Our Sotn ureterorenoscope® has several important features. Firstly, the main mechanical requirements are as follows. The standard ureteroscope connected to the modified UAS was inserted into the upper ureter or renal pelvis guided by the zebra guidewire under direct vision. During the operation, the surgeon can adjust the rotary knob to control the negative pressure and actively control the pressure of the suction of stones for simultaneous reduction of the pressure inside the pelvis and active suction of the stones. The surgery was easily performed using Sotn ureterorenoscope® that was improved by a ureteroscope. Lastly, our system was placed distal to the stone to fragment it. The use of suction evacuation had the advantage of removing all stone fragments without requiring a stone basket and thus shortened the operation time. Our results suggest that only one patient failed the intraoperative placement of the UAS in the first stage of surgery due to ureteral kink and stricture. We also achieved 89.7% immediate SFR and 100% SFR after 1 month in all patients.

This study indicated that the one-time success rate of the modified UAS placement was 98.6%, which is higher than the value (78%) reported by Sabnis et al. (8); the higher value in our work could be due to the fact that most medical specialists have become familiar with rigid ureteroscopy and have enriched experience. For flexible ureteroscopy, placing the modified UAS is often difficult due to uncertainty inside the ureter. Once resistance is encountered, beginners easily fail to place the sheath. Secondly, the standard ureteroscope connected to the modified UAS was inserted into the upper ureter or renal pelvis guided by the zebra guide wire under direct vision to minimize the risk of ureteral injury. Although no damage of the renal pelvis and ureteral wall was observed, the surgeon should be careful to avoid ureter perforation and avulsion during the operation because the modified UAS of the Sotn ureterorenoscope® consists of metal materials. Thirdly, active suction can decrease the pressure in the renal pelvis and reduce postoperative infection rate. The controllable negative-pressure suction system adopted by the Sotn ureterorenoscope® can be controlled by the surgeon during surgery. The postoperative fever rate of this group was 1.9%, and no sepsis occurred. However, in literature, the postoperative fever rate is slightly higher (10.7%) and the rate of septicaemia is 3.4% (9). This finding confirms the various effects of the controllable negative-pressure system. When difference exists between classical surgical methods, randomised controlled studies with large sample size are needed. Finally, through active suction by negative pressure during surgery, the stone fragments can be directly suctioned in the sheath of the modified UAS. In our study, SFR values of patients in late cases were significantly higher than those in early cases and can be further improved by increasing the number of cases.

This study also displayed limitations that must be acknowledged before accepting the findings. The retrospective design employed has disadvantages regarding potential risk of bias. We plan to perform a multicentre, prospective randomised controlled trial with larger sample size in the future. The number of cases treated and evaluated with this system was reasonably low to derive certain, reliable outcomes. Finally, the developed Sotn ureterorenoscope® cannot achieve real-time monitoring of the actual renal pelvic pressure and should be further improved in the future.

CONCLUSIONS

The developed Sotn ureterorenoscope® is safe, feasible and efficient for managing renal or ureter stones because of its advantages of low rate of ureteral injury, high efficacy in stone clearance, improved visual field, short operative time and ease of operation.

FUNDING

This work was supported by Grants from National Natural Science Foundation of China (no. 61301294).

ETHICAL APPROVAL

This clinical trial was approved by the Ethic Committee of The Second Affiliate Hospital of Guangzhou University of Chinese Medicine and conducted under their supervision. Patients were informed that this was a new technique. The risks and benefits were explained and written informed consent was obtained from each of the participants or their legal guardians. Furthermore, the modified sheaths and specimen collection bottles were provided free of charge.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bader MJ, Eisner B, Porpiglia F, Preminger GM, Tiselius HG. Contemporary management of ureteral stones. Eur Urol. 2012;61:764-72.
2. Mugiya S. [Guidelines on urolithiasis: update of diagnosis and treatment]. Hinyokika Kiyo. 2012;58:703-6.
3. Albala DM, Assimos DG, Clayman RV, Denstedt JD, Grasso M, Gutierrez-Aceves J, et al. Lower pole I: a prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy for lower pole nephrolithiasis-initial results. J Urol. 2001;166:2072-80. Erratum in: J Urol 2002;167:1805.
4. Sener NC, Imamoglu MA, Bas O, Ozturk U, Goktug HN, Tuygun C, et al. Prospective randomized trial comparing shock wave lithotripsy and flexible ureterorenoscopy for lower pole stones smaller than 1 cm. Urolithiasis. 2014;42:127-31.
5. Chen S, Fu N, Cui W, Zhao Z, Luo X. Comparison of stone dusting efficiency when using different energy settings of Holmium: YAG laser for flexible ureteroscopic lithotripsy in the treatment of upper urinary tract calculi. Urol J. 2019;0:4955.
6. Legemate JD, Kamphuis GM, Freund JE, Baard J, Zanetti SP, Catellani M, et al. Durability of Flexible Ureteroscopes: A Prospective Evaluation of Longevity, the Factors that Affect it, and Damage Mechanisms. Eur Urol Focus. 2019;5:1105-1111.
7. Resorlu B, Oguz U, Resorlu EB, Oztuna D, Unsal A. The impact of pelvicaliceal anatomy on the success of retrograde intrarenal surgery in patients with lower pole renal stones. Urology. 2012;79:61-6.
8. Sabnis RB, Jagtap J, Mishra S, Desai M. Treating renal calculi 1-2 cm in diameter with minipercutaneous or retrograde intrarenal surgery: a prospective comparative study. BJU Int. 2012;110(8 Pt B):E346-9.
9. Tefekli A, Ali Karadag M, Tepeler K, Sari E, Berberoglu Y, Baykal M, et al. Classification of percutaneous nephrolithotomy complications using the modified clavien grading system: looking for a standard. Eur Urol. 2008;53:184-90.
10. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69:475-82.
11. Kumar U, Tomar V, Yadav SS, Priyadarshi S, Vyas N, Agarwal N, et al. STONE score versus Guy's Stone Score - prospective comparative evaluation for success rate and complications in percutaneous nephrolithotomy. Urol Ann. 2018;10:76-81.
12. Aboutaleb H, Omar M, Salem S, Elshazly M. Management of upper ureteral stones exceeding 15 mm in diameter: Shock wave lithotripsy versus semirigid ureteroscopy with holmium:yttrium-aluminum-garnet laser lithotripsy. SAGE Open Med. 2016;4:2050312116685180.
13. Mursi K, Elsheemy MS, Morsi HA, Ali Ghaleb AK, Abdel-Razzak OM. Semi-rigid ureteroscopy for ureteric and renal pelvic calculi: Predictive factors for complications and success. Arab J Urol. 2013;11:136-41.
14. Khoder WY, Bader M, Sroka R, Stief C, Waidelich R. Efficacy and safety of Ho:YAG laser lithotripsy for ureteroscopic removal of proximal and distal ureteral calculi. BMC Urol. 2014;14:62.
15. Turkan S, Ekmekcioglu O, Irkilata L, Aydin M. Is semirigid ureteroscopy sufficient in the treatment of proximal ureteral stones? When is combined therapy with flexible ureteroscopy needed? Springerplus. 2016;5:30.
16. Li H, Na W, Li H, Jiang Y, Gu X, Zhang M, et al. Percutaneous nephrolithotomy versus ureteroscopic lithotomy for large (>15 mm) impacted upper ureteral stones in different locations: is the upper border of the fourth lumbar vertebra a good indication for choice of management method? J Endourol. 2013;27:1120-5.
17. Guohua Zeng, Jiasheng Li, Zhijian Zhao, et al. Efficacy and safety of retrograde flexible ureteroscopic lithotripsy with holmium:YAG laser in the treatment of renal stones. Chinese Journal of Urology. 2015;6:401–404.
18. Giusti G, Proietti S, Villa L, Cloutier J, Rosso M, Gadda GM, et al. Current Standard Technique for Modern Flexible Ureteroscopy: Tips and Tricks. Eur Urol. 2016;70:188-194.
19. Deng X, Song L, Xie D, Fan D, Zhu L, Yao L, et al. A Novel Flexible Ureteroscopy with Intelligent Control of Renal Pelvic Pressure: An Initial Experience of 93 Cases. J Endourol. 2016;30:1067-1072.

20. Mogilevkin Y, Sofer M, Margel D, Greenstein A, Lifshitz D. Predicting an effective ureteral access sheath insertion: a bicenter prospective study. J Endourol. 2014;28:1414-7.
21. Traxer O, Thomas A. Prospective evaluation and classification of ureteral wall injuries resulting from insertion of a ureteral access sheath during retrograde intrarenal surgery. J Urol. 2013;189:580-4.
22. Sabnis RB, Ganesamoni R, Doshi A, Ganpule AP, Jagtap J, Desai MR. Micropercutaneous nephrolithotomy (microperc) vs retrograde intrarenal surgery for the management of small renal calculi: a randomized controlled trial. BJU Int. 2013;112:355-61.

Correspondence address:
Shusheng Wang, MD
Department of Urology,
The Second Affiliate Hospital of Guangzhou
University of Chinese Medicine, Guangzhou, China
E-mail: shushengwanggzy@163.com

EDITORIAL COMMENT

Vol. 46 (5): 794-795, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0521.1

Editorial Comment: Novel semirigid ureterorenoscope with irrigation and vacuum suction system: introduction and initial experience for management of upper urinary calculi

Eduardo Mazzucchi [1]

[1] *Departamento de Endourologia, Divisão de Urologia, Faculdade de Medicina de São Paulo da Universidade de São Paulo, SP, Brasil*

COMMENT

The authors report their experience with a new semirigid scope attached to an irrigation and suction system with the aim of reducing residual fragments and improving the stone-free rates after ureteroscopy for upper ureteral and renal stones (1).

It is well-known by endourologists that elevated intra-renal pressure during the procedure and residual fragments are two of the main problems of ureteroscopy, once they can lead to sepsis and to asymptomatic residual fragments that result in unexpected visits to the emergency room, re-admittances to the hospital and re-interventions in up to 29 % of the cases (2). Therefore, a search for effective suctioning systems attached to the ureteral access sheath in order to reduce intrapelvic pressure during the procedure and the occurrence of residual fragments after breaking the stone has been reported in the literature (3).

Herein the authors report their experience with a suctioning system coupled to a metallic 40 cm long and 11.6/12.9 Fr diameter access sheath and use a 46 cm and 4/6 Fr mini-ureteroscope inside to treat upper ureteral, pelvic, upper and medium calyceal kidney stones. They treated 58 patients with an 89.7% stone-free rate at 1st PO at CT and 1.7% complication rate. The access sheath could not be inserted in only one patient. Interestingly, the stone was located in the mid-calyx in 19% of the cases and the authors did not report any difficulty or failure in reaching out the calyx with a semirigid device inside a metallic access sheath which is recognizably a difficult task.

Other articles evaluating suctioning access sheaths for big upper ureteral stones have been published showing better stone-free rates when compared to the traditional ones (4).

Suctioning systems seems to be in the near horizon in ureteroscopy but this is an initial experience with a small number of cases performed in a single center. It has to pass the test of time to be incorporated in the daily urological practice.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Gan S, Guo Z, Zou Q, Gu C, Xiang S, Li S, Ye Z, Wang S. Diagnosis accuracy of PCA3 level in patients with prostate cancer: a systematic review with meta-analysis. Int Braz J Urol. 2020;46:786-93.
2. Matlaga BR, Chew B, Eisner B, Humphreys M, Knudsen B, Krambeck A, et al. Ureteroscopic Laser Lithotripsy: A Review of Dusting vs Fragmentation with Extraction. J Endourol. 2018;32:1-6.
3. Deng X, Song L, Xie D, Fan D, Zhu L, Yao L, et al. Novel Flexible Ureteroscopy with Intelligent Control of Renal Pelvic Pressure: An Initial Experience of 93 Cases. J Endourol. 2016t;30:1067-72.
4. Zhu Z, Cui Y, Zeng F, Li Y, Chen Z, Hequn C. Comparison of suctioning and traditional ureteral access sheath during flexible ureteroscopy in the treatment of renal stones. World J Urol. 2019;37:921-9.

Eduardo Mazzucchi, MD

Departamento de Endourologia,
Divisão de Urologia, Faculdade de Medicina de São Paulo da Universidade de São Paulo, São Paulo, SP, Brasil
E-mail: emazzucchi20@gmail.com

ARTICLE INFO

Eduardo Mazzucchi
https://orcid.org/0000-0003-3870-5922
Int Braz J Urol. 2020; 46: 794-5

Submitted for publication:
March 15, 2020

Accepted:
March 30, 2020

ORIGINAL ARTICLE

Vol. 46 (5): 796-802, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0571

Development and validation a task-specific checklist for a microsurgical varicocelectomy simulation model

Marcelo Esteves Chaves Campos [1], Marcelo Magaldi Ribeiro de Oliveira [1], Augusto Barbosa Reis [1], Lilian Bambirra de Assis [2], Viacheslav Iremashvili [3]

[1] Departamento de Cirurgia, Universidade Federal de Minas Gerais - UFMG, Belo Horizonte, MG, Brasil; [2] Departamento de Ciências Sociais Aplicadas, CEFET, Belo Horizonte, MG, Brasil; [3] Department of Urology, United Hospital Center, Bridgeport, West Virginia, USA, United States

ABSTRACT

Purpose: To develop and validate a new test of specific technical skills required for microsurgical varicocelectomy.
Materials and Methods: An electronic questionnaire was sent to 558 members of the Brazilian Society of Urology for the validation of the task-specific checklist (TSC) for assessment of microsurgical varicocelectomy. Participants who had experience in this procedure were selected as judges. For construct validation, 12 participants including attending urologists and urological residents in training were recruited for voluntary participation. We formed a group of three experts and a group of nine novices, who had to perform the steps of microsurgical varicocelectomy on a simulation model using human placenta. Each participant was filmed and two blinded raters would then evaluate their performance using the TSC of microsurgical varicocelectomy.
Results: 14 judges were recruited. The assessment tool was reformulated, according to the judges suggestions and had the content validity achieved. The final version of the TSC was comprised of the task-specific score, a series of 4 items scored in a binary fashion designed for microscopic sub-inguinal varicocelectomy. The differences between the performance of participants with different levels of experience reflected the construct validity. The reliability between the raters was high. The mean time required to complete the training of microsurgical varicocelectomy in simulation model was significantly shorter for experts compared to novices (201 vs. 496 seconds, p=0.01).
Conclusions: This preliminary study suggests that the task-specific checklist of microsurgical varicocelectomy is reliable and valid in assessing microsurgical skills.

ARTICLE INFO

Marcelo Esteves C Campos
http://orcid.org/0000-0002-8093-8052

Keywords:
Simulation Training; Educational Measurement; Microsurgery

Int Braz J Urol. 2020; 46: 796-802

Submitted for publication:
September 05, 2019

Accepted after revision:
January 18, 2020

Published as Ahead of Print:
April 10, 2020

INTRODUCTION

Since the classic work of Tulloch, varicoceles are known to be associated with male factor infertility (1). Surgical correction of varicoceles improves the rate of spontaneous pregnancy making this disease the most important surgically correctable cause of infertility in males (2). Some other less common indications for varicocelectomy include testicular pain and testicular dysfunction (3).

Marmar, Debenedictis & Praiss (1985) described the microdissection of the spermatic cord at the external inguinal ring for the management of varicoceles (4). Since then, the use of microsurgical techniques has been widely adopted, improving results and reducing surgical complications

by allowing better identification and preservation of lymphatics and testicular arteries (5). Although sub-inguinal microsurgical varicocelectomy is currently considered the gold standard treatment for varicocele, microsurgical manipulations are not parts of the skill set of many urologists making this procedure challenging (6).

The steep learning curve in the acquisition of microsurgical skills defines the need for training outside of the operating room (7). Training in the laboratory on simulation models may help providers develop familiarity with micro instruments handling, as well as cognitive and technical competency in microsurgery (8, 9).

Several models have been proposed in teaching and learning of microsurgery practice (10, 11). While assessment of learning skills and abilities gained by the trainees is imperative (12-14), to our knowledge there are no published studies reporting simulation in evaluation of surgical skills in microsurgical varicocelectomy. The purpose of this study was to fill this gap by developing and validating such a test of specific technical skill for microsurgical varicocelectomy simulation model.

MATERIALS AND METHODS

This study received an approval from a certified Ethical Board and 12 human placentas were collected. The expectant mothers underwent prenatal infectious evaluation and signed consent for donation of placenta for practice in surgical techniques.

The study was divided into three stages. Firstly, a simulation model for the training of microsurgical varicocelectomy was built. Then, a task-specific checklist for assessment of microsurgical varicocelectomy (TSC) was developed. Lastly, a validation study was carried out to determine the reproducibility, reliability and validity of this tool.

Simulation model

The average human placenta has a diameter of 17.0 to 19.0cm and a thickness of 2.0 to 3.0cm. The allantoid membrane covers the fetal surface. The umbilical cord usually contains two arteries and one vein and the vessels radiate on the fetal surface with diameters ranging from 1.22 to 12.27mm (15).

Placentas were washed with 0.9% saline to remove any blood from their surfaces. The umbilical cords were shortened to 8cm to allow easy catheterization of the umbilical arteries and vein. A 6 French gauge urinary catheter was used to catheterize the umbilical vessels and a 0.9% saline was used to irrigate the specimen until the vessels were free of blood clots.

Placenta was spread over the operative table, with the fetal surface facing upward. The initial step was to choose a placental vein irrigation area that also included a placental artery to build the simulation model. Cutting 1.0cm deep into the placental stroma around this predetermined region, the placenta was folded inwards to simulate the spermatic funiculus (Figure-1A). This reconstructed funiculus was sutured using a 3-0 Vycril (Figure-1B). The main artery and vein were cannulated with a 6 French gauge urinary catheter and continuous infusion of colored saline solutions (red for artery and blue for vein -0 Gouache 1:10 saline) was started to simulate blood (Figure--1C). Since the placenta vascular tree has just one flow direction, the infused fluid flowed out through the placenta stroma into a bowl connected to a drainage system.

Development of task-specific checklist

A task-specific checklist for assessment of microsurgical varicocelectomy was developed, consisting of 7 items scored in a binary fashion (not done/done incorrectly=0 or done correctly=1). These items correspond to important steps of the procedure (Figure-2) and evaluate the technical ability of the provider in performing sub--inguinal microsurgical varicocelectomy. The items were as follows: 1) Keep the sterile field and use the microscope properly; 2) Use the micro--instruments correctly; 3) Recognize and correctly dissect the spermatic fascia for access to the vessels; 4) Correctly identifies arteries and veins; 5) Adequately performs the dissection of the dilated veins; 6) Adequately performs the ligatures of the dilated veins; 7) Adequately performs the dilated veins section.

Figure 1 - Surgical preparation of human placenta in a varicocele model. A) Cutting 1.0 cm deep and folding the placenta stroma. B) Suturing the folded borders. C) Spermatic funiculus simulation.

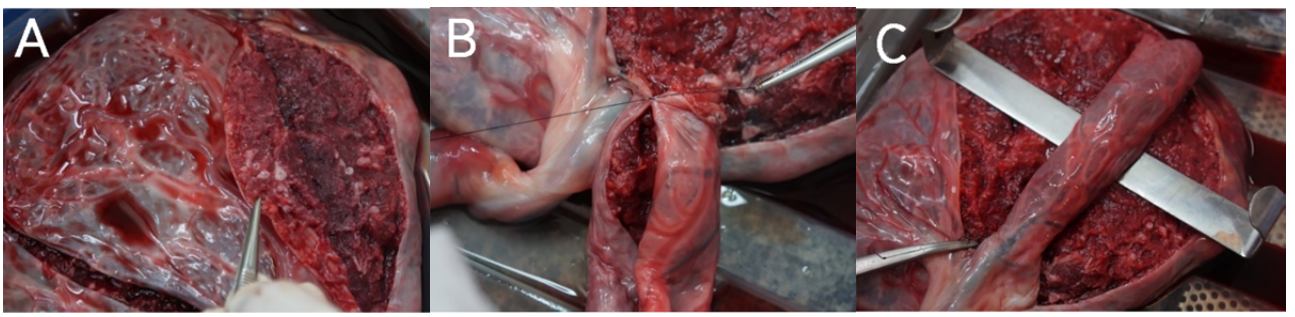
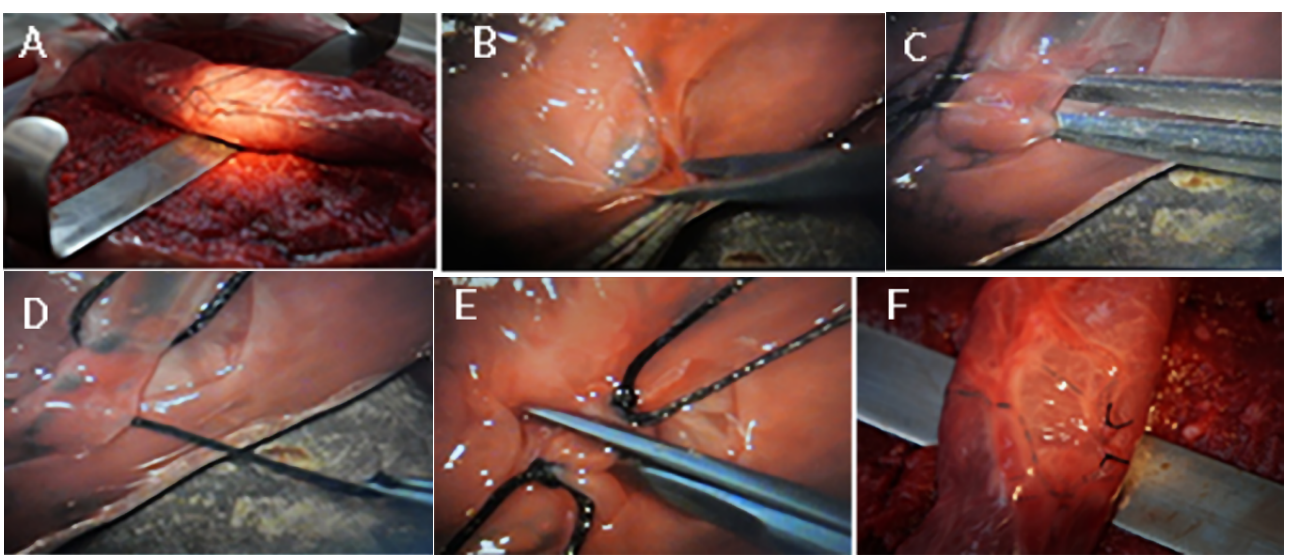


Figure 2 - Microsurgical handling of placenta vessels simulating the varicocele treatment. A) Simulated spermatic funiculus put under microscopic working area. B) Allantoic membrane dissection for access to the placenta vessels. C) Placenta vein dissection, after identify artery. D) Placenta vein knot tying. E) Placenta vein micro-scissors cutting. F – Final appearance of vein cutting in the simulated spermatic funiculus.



Then, an electronic questionnaire was sent to 558 members of the Brazilian Society of Urology for the validation of the tool. Participants who performed more than ten microsurgical varicocelectomy per year were selected as judges.

Validation task-specific checklist

All judges filled out a post-study questionnaire to assess TSC usefulness as an evaluation tool. The items of the test were evaluated (content validity), considering five requirements: pertinence, feasibility, objectivity, clarity and vocabulary. The questionnaires were presented on a 3-point scale (1) Adequate; 2) Adequate with changes; 3) Inadequate). The tool was reformulated, according to the judges suggestions and the final version of the task-specific checklist was created.

For construct validation, 12 participants including urologists and residents in training for urology were recruited for voluntary participation. Two groups were formed based on the microsurgical experience. Group 1 consisted of three urologists who performed more than 100 microsurgical procedures each (Expert group) and group 2 included nine urology residents with little microsurgical experience (performed at most 10 microsurgical procedures; Novice group). The subjects were given a standardized explanation

about the surgical steps of the microscopic sub-inguinal varicocelectomy showing a varicocele surgical treatment video and then administered a practice round in the simulation model. Each participant wore a surgical hair net, a face mask and a surgical gown. Each urologic surgery was filmed, with special attention to camera framing so as to film only the hands of the operator during the maneuvers, for anonymization purposes. The videos were then viewed by two educational experts who were unaware of the group assignment. The two education experts also had experience in microsurgical varicocelectomy, but were different from the judges. They rated the participants independently. To evaluate the construct validity, they used the final version of the TSC to compare the performance of participants with different levels of experience. The time required to complete the activity was also measured and compared between the groups.

RESULTS

Of the 558 questionnaires sent, we received 49 responses eight of which were incomplete. Of the 41 eligible responses, only 14 participants had the surgical microscope available and used it to perform varicocelectomy. These were recruited as judges.

Assessment of content validity of the TSC resulted in five out of 7 items being considered Adequate or Adequate with changes by all 14 judges. The other two items (6 and 7) were evaluated as Inadequate by a single judge.

The judges felt that some items were redundant and should be merged to facilitate the assessments. They also suggested that the handling of microsurgical instruments should not be assessed separately and that this skill should be evaluated throughout all tasks. The tool was reformulated, according to the judges suggestions and reduced to four items. Table-1 presents the final version of the TSC was comprised of the task-specific score, a series of 4 items scored in a binary fashion designed for microscopic sub-inguinal varicocelectomy.

Figure 3 shows the differences between experts and novices reflecting the construct validity. The concordance of the scores between the educational experts was not full due to the item "Properly recognizes and dissects fascia for access to the vessels?", which had only 50% concordance. However, the other three items had an agreement of 100% in the educational experts scores. Moreover, the reliability between the two educational experts, among the Novice group, for which there were disagreements, was full, since both returned the same rank of the nine novices. The mean time required to complete the training of microsurgical varicocelectomy in simulation model was significantly shorter for experts compared to novices (201 vs. 496 seconds, p=0.01).

DISCUSSION

Microsurgical correction is the standard treatment for varicocele, however familiarity of the urologists with the technical skills necessary for this procedure remains limited (16). The traditional learning model, in which the apprentice observes, assists and finally operates under the supervision of the tutor, requires a long period of training in order to reach the expertise (17). In the modern surgical era simulation training models are becoming a crucial step in the progress of the apprentice towards performing live operations (18). Human placenta was described as a training tool in microsurgery in 1979 when it was used for cutting and suturing vessels without any previous preparation (19). The simulation model used in this study reproduces anatomical conditions encountered during the microsurgical varicocelectomy and recreates a clinical experience without risking patient's health. As important as the teaching method is the assessment of the learning abilities and skills acquired by the trainees (20). This is the first study that developed and validated a task-specific checklist for assessment of microsurgical varicocelectomy.

The use of an electronic questionnaire in the initial phase of validation of the tool offers many advantages including low cost and user-friendly format easing the recruitment of judges. The main downside is the low response rate. According to Dainesi & Goldbaum (2012), the average response rate of the questionnaires

Table 1 - Final version of the task-specific checklist for microsurgical varicocelectomy.

INSTRUCTIONS TO PARTICIPANTS You have just come across a varicocelectomy simulation model built using human placenta. The operating microscope was taken to the surgical field. Under a magnification of 12 x, you should open the allantoid membrane, simulating the spermatic fascia, and identify the artery and the veins. Then you should dissect, perform a double ligation and cut a vein.			
CHECKLIST			
ITEM		**NOT DONE/ DONE INCORRECTLY**	**DONE CORRECTLY**
1	Adjusts, position and correctly handles the microscope, keeping the sterile field?	0	1
2	Properly recognizes and dissects fascia for access to the vessels?	0	1
3	Adequately performs the dissection of the dilated veins, differentiating them from the arteries and lymph vessels?	0	1
4	Adequately performs vein ligatures and vein section?	0	1
TOTAL SCORE		/ 4	
TIME NEEDED TO COMPLETE		**SECONDS**	

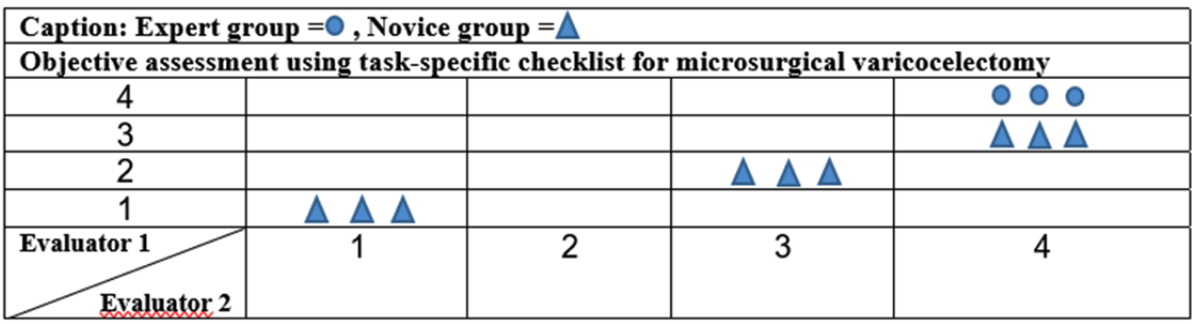
via e-mail is 8.2% (21) which is similar to 8.8% observed in our study.

The high concordance between the judges in the evaluation of the TSC items for the assessments considered Adequate or Adequate/Adequate with changes supports the content validity of the tool. Evaluation of the construct validity demonstrated clear performance differences between the experts and novices. The longer time required by novices to perform the tasks suggests that the model may be used to evaluate and improve microsurgical skills required for the actual procedure, although this remains to be proven.

The concordance measures how often the two educational experts attribute exactly the same score, while the reliability measures the relative similarity between the two sets of ratings. There was disagreement between the two raters among the Novice group in the item "Properly recognizes and dissects fascia for access to the vessels?", with consequent leveling of the skills of three novices with that of the experts by evaluator 2. Despite this, the reliability between the two educational experts remained high. The vessels in the spermatic funiculus are surrounded by fascia and fatty tissue. In the placenta model they are surrounded by allantoid membrane and placenta stroma. Thus, one of the possible explanations for the discordance for the item "Properly recognizes and dissects fascia for access to the vessels?" was the differences between the educational experts in their perception of the similarity between the allantoid of the human placenta and the spermatic fascia.

The main methodological limitations of this research are the single-center design and small number of providers in both expert and novice groups. It should be noted that our ability

Figure 3 - Concordance of the scores between the Educational Experts and construct validity.



to recruit participants for the former group was limited by the shortage of urologists with microsurgical skills in Brazil. In addition, another limitation was that the electronic questionnaire for the selection of judges was sent only to a portion of Brazilian urologists, being a convenience sample. However, despite this selection bias, we believe it was a representative sample.

CONCLUSIONS

This preliminary study suggests that the task-specific checklist of microsurgical varicocelectomy is reliable and valid in assessing surgical skills when used in the settings of human placental simulation model.

ACKNOWLEDGMENT

We thank all the expectant mothers who donated the placentas for practice in surgical techniques, residents and experts for participating in the research.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Marte A. The history of varicocele: from antiquity to the modern ERA. Int Braz J Urol. 2018;44:563-76.
2. Esteves SC, Glina S. Recovery of spermatogenesis after microsurgical subinguinal varicocele repair in azoospermic men based on testicular histology. Int Braz J Urol. 2005;31:541-8.
3. Altunoluk B, Soylemez H, Efe E, Malkoc O. Duration of preoperative scrotal pain may predict the success of microsurgical varicocelectomy. Int Braz J Urol. 2010;36:55-9.
4. Marmar JL, DeBenedictis TJ, Praiss D. The management of varicoceles by microdissection of the spermatic cord at the external inguinal ring. Fertil Steril. 1985;43:583-8.
5. Wang J, Xia SJ, Liu ZH, Tao L, Ge JF, Xu CM, et al. Inguinal and subinguinal micro-varicocelectomy, the optimal surgical management of varicocele: a meta-analysis. Asian J Androl. 2015;17:74-80.
6. Trignano E, Fallico N, Zingone G, Dessy LA, Campus GV. Microsurgical Training with the Three-Step Approach. J Reconstr Microsurg. 2017;33:87-91.
7. Mehta A, Li PS, Goldstein M. Male infertility microsurgical training. Transl Androl Urol. 2014;3:134-41.
8. Ghanem AM, Hachach-Haram N, Leung CC, Myers SR. A systematic review of evidence for education and training interventions in microsurgery. Arch Plast Surg. 2013;40:312-9.
9. Grober ED, Hamstra SJ, Wanzel KR, Reznick RK, Matsumoto ED, Sidhu RS, et al. Laboratory based training in urological microsurgery with bench model simulators: a randomized controlled trial evaluating the durability of technical skill. J Urol. 2004;172:378-81.
10. Dumestre D, Yeung JK, Temple-Oberle C. Evidence-based microsurgical skill-acquisition series part 1: validated microsurgical models--a systematic review. J Surg Educ. 2014;71:329-38.
11. Pinto LOAD, de Barros CAV, de Lima AB, Dos Santos DR, de Bacelar HPH. Portable model for vasectomy reversal training. Int Braz J Urol. 2019;45:1013-1019.

12. Campos MEC, Oliveira MMR, Assis LB, Reis AB, Gonçalves FB. Validation of the Objective Structured Assessment of Technical Skill in Brazil. Rev Assoc Med Bras (1992). 2019. In press.
13. Dumestre D, Yeung JK, Temple-Oberle C. Evidence-based microsurgical skills acquisition series part 2: validated assessment instruments--a systematic review. J Surg Educ. 2015;72:80-9.
14. Morris C, Hoogenes J, Shayegan B, Matsumoto ED. Towards development and validation of an intraoperative assessment tool for robot-assisted radical prostatectomy training: results of a Delphi study. Int Braz J Urol. 2017;43:661-670.
15. Oliveira MM, Wendling L, Malheiros JA, Nicolato A, Prosdocimi A, Guerra L, et al. Human Placenta Simulator for Intracranial-Intracranial Bypass: Vascular Anatomy and 5 Bypass Techniques. World Neurosurg. 2018;119:e694-e702.
16. Cho CL, Ho KL, Chan WK, Chu RW, Law IC. Use of indocyanine green angiography in microsurgical subinguinal varicocelectomy - lessons learned from our initial experience. Int Braz J Urol. 2017;43:974-979.
17. Aydin A, Shafi AM, Shamim Khan M, Dasgupta P, Ahmed K. Current Status of Simulation and Training Models in Urological Surgery: A Systematic Review. J Urol. 2016;196:312-20.
18. O'Shea JS. Becoming a surgeon in the early 20th century: parallels to the present. J Surg Educ. 2008;65:236-41.
19. Goldstein M. Use of fresh human placenta for microsurgical training. J Microsurg. 1979;1:70-1.
20. Shaharan S, Neary P. Evaluation of surgical training in the era of simulation. World J Gastrointest Endosc. 2014;6:436-47.
21. Dainesi SM, Goldbaum M. E-survey with researchers, members of ethics committees and sponsors of clinical research in Brazil: an emerging methodology for scientific research. Rev Bras Epidemiol. 2012;15:705-13.

Correspondence address:
Marcelo Esteves Chaves Campos, MD
Departamento de Cirurgia,
Universidade Federal de Minas Gerais - UFMG
Rua Congonhas 792 / 301, Santo Antônio
Belo Horizonte, MG, 30330-100, Brasil
Tel.: 55 31 991967784
E-mail: camposmec@yahoo.com.br

EDITORIAL COMMENT

Vol. 46 (5): 803-804, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0571.1

Editorial Comment: Development and validation a task-specific checklist for a microsurgical varicocelectomy simulation model

Rodrigo R. Vieiralves [1]

[1] *Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil*

COMMENT

Microsurgery training is far from becoming a reality in the urologist practice. Due to the limitations of its application and aiming to increase the accessibility of this important tool, some experimental models have emerged over time (1, 2). In this very interesting article conducted at CEFET and Federal University of Minas Gerais, Brazil, a task-specific checklist of technical skills for microsurgical varicocelectomy was developed (3). As we know, a varicocele is an abnormal dilation of the pampiniform plexus of the testis. In up to 40% of infertile men, a palpable varicocele is found, while the prevalence of a varicocele in the general male population is about 15%. The benefit of varicocele repair must be weighed by the risk associated with the procedure, so it is important to select the procedure with the greatest success and lowest rate of complications. Microsurgical varicocelectomy, low inguinal or subinguinal (4), is preferred by many urologists and specialists in male infertility, as it is associated with a higher success rate, facilitating the identification of vascular structures and lymphatic vessels (5, 6). The surgery involves a complex number of factors for its true success. The preparation of the surgical field itself with the correct use of the microscope, the identification of vascular structures such as spermatic arteries and veins and also the lymphatic vessels with the correct handling of these structures are very important. In this context, this paper becomes naturally relevant, as it deals with a field that is still little explored in our specialty, with microsurgical ability still being an entry barrier to urological development in this scenario.

In this article with carefully elaborated methodology, a validated checklist was developed, allowing the assessment of surgical skills in the microsurgical treatment of varicocelectomy. Based on 4 requirements (handling the microscope, recognition of the fascia and identification of vessels, correct dissection and differentiation between arteries and veins, ligatures and the section of the vessels) was given a note regarding the performance in this technique, allowing to evaluate microsurgical abiliity in the treatment of varicocele.

However, some relevant aspects need to be highlighted. First we will refer to the simulation model used: The model used a human placenta that was prepared to simulate the spermatic cord. In addition to the difficulty in accessing placental tissue by the urological community, the consistency of this reconstructed funicle through a placental incision with allantoic membrane coating is unlikely to simulate the consistency of the external spermatic fascia. In the article, we did not identify the exact region of the placenta that should be chosen. It should include a placental artery but without reporting if it should be more proximal or distal to the umbilical cord. We understand that, according to the region of the placenta, the vascular net can in theory present different caliber, impacting on a non-realistic model. The vessels were also perfused with a dye solution (red for artery and blue for vein) which, in theory, would facilitate the diagnosis of an arterial or venous vascular structure. With regard to the development of the check list, it is noteworthy that only 14 urologists had previous practice in microvaricocelectomy and with a small experience (10 procedures / year). As they were recruited as judges in the elaboration of the questionnaire, we consider the "n" not high enough and it would be possible that aspects relevant to the procedure were left out. Also, during the construction

of the validation, the presence of only two educational experts can also compromise the validation. Ideally, the agreement of a third expert could have been included in the experiment, increasing the reliability. Still, nothing about statistical tests for validation or reliability analysis was mentioned. Another point that should be mentioned is the low number of participants in the model and the simulation with only nine residents of the same service. We understand that results based on training of only 9 residents can present an important bias, due to individual aspects besides the fact that they are part of the same Hospital (similar previous training), making the external validation of this model difficult.

To conclude, we see in this important paper the presentation of task-specific check list for a microsurgical varicocelectomy simulation model, that is reproducible and quickly applicable. It allows assessment of surgical skills and thus offers an evaluation method of the stage of progression in the microsurgical varicocelectomy training process. Being an unprecedented model, we understand that it can serve as a basis for new checklists and realistic simulation models in the scenario of microsurgery applied to urology.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Pinto LOAD, de Barros CAV, de Lima AB, Dos Santos DR, de Bacelar HPH. Portable model for vasectomy reversal training. Int Braz J Urol. 2019;45:1013-9.
2. Hayden RP, Li PS, Goldstein M. Microsurgical vasectomy reversal: contemporary techniques, intraoperative decision making, and surgical training for the next generation. Fertil Steril. 2019;111:444-53.
3. Campos MEC, de Oliveira MMR, Reis AB, de Assis LB, Iremashvili V. Development and validation a task-specific checklist for a microsurgical varicocelectomy simulation model. Int Braz J Urol. 2020;46:796-802.
4. Marmar JL, DeBenedictis TJ, Praiss D. The management of varicoceles by microdissection of the spermatic cord at the external inguinal ring. Fertil Steril. 1985;43:583?8.
5. Goldstein M, Gilbert BR, Dicker AP, Dwosh J, Gnecco C. Microsurgical inguinal varicocelectomy with delivery of the testis: an artery and lymphatic sparing technique. J Urol. 1992;148:1808-11.
6. Cayan S, Kadioglu TC, Tefekli A, Kadioglu A, Tellaloglu S. Comparison of results and complications of high ligation surgery and microsurgical high inguinal varicocelectomy in the treatment of varicocele. Urology. 2000;55:750-4.

Rodrigo R. Vieiralves, MD

Serviço de Urologia, Hospital Federal da Lagoa,
Rio de Janeiro, RJ, Brasil
E-mail: rrvieiralves@gmail.com

ARTICLE INFO

Rodrigo Vieiralves
https://orcid.org/0000-0003-4745-0319
Int Braz J Urol. 2020; 46: 803-4

Submitted for publication:
April 15, 2020

Accepted:
April 20, 2020

ORIGINAL ARTICLE

Vol. 46 (5): 805-813, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0797

Study of serum and urinary markers of the renin-angiotensin-aldosterone system in myelomeningocele patients with renal injury detected by DMSA

Cássia Maria Carvalho Abrantes do Amaral [1], Dulce Elena Casarini [1], Maria Cristina Andrade [1], Marcela Leal da Cruz [2], Antônio Macedo Jr. [1, 2]

[1] Departamento de Pediatria, Universidade Federal de São Paulo - UNIFESP, São Paulo, SP, Brasil; [2] Departamento de Urologia, Centro de Apoio à Criança com Anomalia Urológica –CACAU - Núcleo de Urologia Pediátrica - NUPEP, São Paulo, SP, Brasil

ABSTRACT

Introduction: The Renin-Angiotensin-Aldosterone System (RAAS) has been suggested as a possible marker of renal injury in chronic diseases. This study proposes to analyze the serum and urinary markers of the RAAS in myelomeningocele patients with renal function abnormalities detected on DMSA.

Material and Methods: Seventeen patients followed in our institution that presented with renal injury on DMSA. We review nephrologic and urologic clinical aspects and evaluated ultrassonagraphy, voiding urethrocystography and urodynamics. Urinary and serum samples were collected to evaluate possible correlations of renal lesions with RAAS. Control group urine and serum samples were also sent for analysis.

Results: Serum ACE 2 activity means in relation to urodynamic findings were the only values that had a statistically significant difference (p = 0.040). Patients with normal bladder pattern presented higher ACE 2 levels than the high risk group. Statistical analysis showed that the study group (SG) had a significantly higher mean serum ACE than the CG. The means of ACE 2 and urinary ACE of the SG and CG were not statistically different. The ROC curve for serum ACE values had a statistically significant area for case and non-case differentiation, with 100% sensitivity and 53% specificity for values above 60.2 mg/dL. No statistically significant areas were observed in relation to ACE 2 and urinary ACE values between SG and CG.

Conclusion: The analysis of serum ACE, ACE 2 and urinary ACE were not significant in patients with myelomeningocele and neurogenic bladder with renal injury previously detected by renal DMSA.

ARTICLE INFO

Marcela Leal da Cruz
http://orcid.org/0000-0002-7087-4534

Keywords:
Meningomyelocele; Acute Kidney Injury; Renin-Angiotensin System

Int Braz J Urol. 2020; 46: 805-13

Submitted for publication:
December 11, 2019

Accepted after revision:
January 16, 2020

Published as Ahead of Print:
April 20, 2020

INTRODUCTION

Myelomeningocele (MMC) is the main pathology associated with neural tube closure defects with an incidence of 1.9 to 3.7 per 10.000 live births (1, 2). It is known that the neurogenic bladder due to this anomaly requires follow-up from birth because of the risk of renal deterioration.

The Renin-Angiotensin-Aldosterone System (RAAS) plays an important role in regulating blood pressure and electrolyte homeostasis through the release of renin by juxtaglomerular cells,

and it has been suggested as a possible marker of renal injury in chronic diseases.

Gobet et al. (3) observed that in fetal-onset renal diseases, as well as in postnatal renal diseases, RAAS played an important role in renal interstitial fibrosis, possibly by activating the transforming growth factor-beta (TGF-β1), which has the function of controlling cell proliferation and differentiation, and other functions in most cells.

This study proposes to analyze the serum and urinary markers of the Renin-Angiotensin--Aldosterone System in myelomeningocele patients with renal function abnormalities detected on DMSA scintigraphy in order to identify whether they can be used as diagnostic and prognostic markers of the kidney damage secondary to bladder abnormalities that may occur in this condition.

MATERIALS AND METHODS

The research was registered and approved by the Research Ethics Committee (REC) of our institution. Eighty-seven patients undergoing regular follow-up were studied at Pediatric Nephrology Outpatient Clinic in our institution. From these, 21 (24%) presented a description in the DMSA renal scintigraphy alteration chart. A blinded reassessment of the examinations was then performed by a specialist in Nuclear Medicine, confirming the change in 17 patients representing the study group (SG). The control group (CG) consists of age-matched patients without urological diseases.

These patients were summoned to a new interview with detailed review of the following parameters: gender, age, antenatal data, voiding habit, intermittent catheterization, use of medications, ventricular-peritoneal shunt, evolution to renal disease (through dosing of serum and urinary urea and creatinine), presence of vesicoureteral reflux, presence of hydronephrosis and bladder thickening, presence of chronic intestinal constipation (Bristol Scale) (4), number of urinary tract infections in the last year, evaluation of systemic blood pressure, evaluation of weight and height according to age and gender.

The presence of pyelonephritis (febrile episode with urine I leukocyte alteration and positive urine culture above 100.000cfu/mL), as well as the need for hospitalization were reported at the initial assessment, and at each visit to the Nephro--pediatric Outpatient Clinic.

Patients were classified according to the stage of renal injury they presented, using the estimated glomerular filtration rate (eGFR) based on the Schwartz equation (2012) updated (5). Patients with eGFR above 90mL/min/1.73m2 were considered without renal function impairment and those with eGFR below 90mL/min/1.73m^2 with alteration.

Technetium-99m-labeled DMSA static renal scintigraphy (99mTc-DMSA) was evaluated according to a study proposed by Ono et al., (6) and classified as: renal uptake greater than 45%: absence of renal injury, renal uptake between 44 to 40%: mild injury, renal uptake between 39 and 35%: moderate injury and renal uptake between 34 and 30%: severe injury.

The renal and urinary tract ultrasound were evaluated for the presence of hydronephrosis and thickening of the bladder walls. Hydronephrosis was classified from grades 1 to 4 according to the classification of the Fetal Urological Society (7). The bladder wall was named normal or hypertrophic (above 3mm) (8). The presence of VUR was assessed by voiding urethro-cystography and classified according to the classification of the International Reflux Study (IRS 1-5) (9).

The urodynamic study (UDS) allowed the update of the bladder pattern classification distributed in the following groups (10): normal pattern, high risk pattern: Patients with Detrusor Leak Point Pressure (DLPP) from 40cm H2O, high detrusor pressure during bladder filling or hyperactivity amplitude from 40cm H2O, incontinent pattern and hypocontractile pattern.

Urinary and serum samples were collected from 17 selected patients to evaluate possible correlations of renal lesions with RAAS. CG urine and serum samples were also sent for analysis to quantify serum Angiotensin-Converting Enzyme (ACE) and Angiotensin-Converting Enzyme 2 (ACE 2) and urinary ACE activities. The urine collected samples were immediately frozen and individually processed after measurement of their volume and pH correction. There was adjustment of pH to 8.0 with Tris buffer 1M and the urine sub-

mitted to centrifuge (3000rpm). ACE activity was determined fluorimetrically using Z-Phe-His-Leu (Z-Phe-HL) as substrate (11). ACE 2 activity in serum was fluorimetrically determined based on the work of Pedersen et al. (12). Sample assays were performed in duplicate, with intrinsic fluorescence corrected by white.

For all statistical tests, a significance level of 5% was used. Statistical analyzes consisted of the Chi-square test, or alternatively in small sample cases, Fisher's exact test. Comparison of means between two independent groups and between two related samples (RG and CG paired by gender and age) were performed respectively by Student's t-tests for independent and paired samples.

Comparison of means between more than two independent groups was performed using the non-parametric Kruskal-Wallis test due to the sample 2 size. At detecting mean differences, the identification of groups with distinct means was performed via Dunn-Bonferroni multiple comparisons to maintain the global significance level.

The ROC curve was used to assess the discriminatory capacity of cases and non-cases of altered DMSA, according to the RAAS activity indicators. Areas under the curve are considered significative in accordance with the p-value <0.05.

RESULTS

Information from 87 patients whose mean age was 8.1 years (SD=6.9 years and range from 4 months to 24 years) was analyzed. From the 87 patients evaluated, 17 (19.5%) had altered DMSA.

The clinical characteristics of the patients studied with DMSA scintigraphy are shown in Table-1. There is a predominance of females (82.4%). It is also noted that almost half of the SG was diagnosed before birth (intrauterine) and 7 out of 10 started treatment at birth. The average gestational age (GA) at birth was 38.2 weeks (SD=1.4 weeks), ranging from 36 to 41 weeks.

In regards to mobility, 35.3% of the SG had good mobility, 29.4% regular and 35.3% bad. It was also observed that 94.1% had no comorbidities, 41.2% presented lumbar injury level and 41.2% sacral level, 88.2% of patients with hydrocephalus and need of VPS in 93.3% of cases. In addition, 94.1% of patients had Bristol score grade 1 and 88.2% were submitted to intermittent bladder catheterization, and in 56.3% of cases, the mother was responsible for performing the procedure. Also regarding urological treatment, 47.1% were on anticholinergics and 58.8% were on antibiotic prophylaxis. The presence of UTI was observed in 82.4% of patients and 23.5% had impaired renal function.

Regarding the findings of nephro-urological imaging exams and urodynamic features of the SG, it was observed the presence of pyelo--calix dilation on USRV in 94.1% of the patients, and in 47.1% the dilation was only pelvic with normal renal parenchyma. In addition, 82.4% of SG had mild or moderate DMSA lesions (similar distribution of mild and moderate lesions). Additionally, 52.9% presented vesicoureteral reflux. The UDS was changed in 76.4%, with 52.9% of patients with incontinent pattern and 23.5% with high risk pattern.

Table-2 shows the activities of serum ACE and ACE 2, and urinary ACE. Serum ACE activity in SG did not show significant changes according to the variables evaluated.

Serum ACE 2 activity means in relation to UDS findings were the only values that had a statistically significant difference (p=0.040) (Table-2). Patients with normal UDS classification presented higher ACE 2 levels than the high risk group. There were no differences in ACE 2 in the incontinent group compared to the other groups. Regarding the association between the ACE, ACE 2 and urinary ACE dosages and the patient's creatinine clearance stage, no statistical differences were observed.

Statistical analysis comparing the results of serum ACE, ACE 2 and urinary ACE between the study (SG) and control (CG) groups showed that the SG had a significantly higher mean serum ACE (106.68nmol/mL/min) than the CG (74.06nmoL/mL/min). The means of ACE 2 and urinary ACE of the patient and control groups were not statistically different.

According to Figure-1, the ROC curve values for serum ACE values had a statistically significant area for case and non-case differentiation, with 100% sensitivity and 53% specificity for serum ACE values above 60.2mg/dL. No statistically significant

Table 1 – Clinical aspects in Study Group (SG).

	Average	SD
Gestational Age (weeks)	38.2	1.4
	N	%
Gender	17	100.0
Female	14	82.4
Male	3	17.6
Mobility		
Good	6	35.3
Regular	5	29.4
Bad	6	35.3
Comorbidity		
Yes (Arterial Hypertension)	1	5.9
No	16	94.1
IMC (kg/m²)		
Eutrophy	11	64.7
Overweight	4	23.5
Obesity	2	11.7
Level of Medular Lesion		
Lumbar	7	41.2
Sacral	7	41.2
Thoracic	5	29.4
Hydrocephalus		
No	2	11,8
Yes	15	88,2
Moment at diagnosis		
Postnatal	8	47.1
Prenatal	9	52.9
Moment at beginning of urological treatment		
At birth	14	82.4
After 1 year old	3	17.6
Clean Intermittent Catheterization (CIC)		
No	1	5.9
Yes	15	88.2
Vesicostomy	1	5.9
Person who peforms CIC		
Mother	9	56.3
Patient	7	43.8
Anticholinergics		
No	9	52.9
Yes	8	47.1
Antibiotic Prophylaxis		
No	7	41.2
Yes	10	58.8
UTI		
No	3	17.6
Yes	14	82.4
Renal Function		
Abnormal	4	23.5
Normal	13	76.5
Bristol Score		
1	16	94.1
5	1	5.9

Table 2 – Serum ACE, ACE 2 and urinary ACE activity in Study Group.

	Average (SD)	Median	n	p
Serum ACE (nmol/mL/min.)				
DMSA				**0.282**
44 to 40 %: Mild lesion	93.81 (27.88)	90.7	7	
39 to 35%: Moderate lesion	116.94 (38.72)	103.6	7	
34 to 30%: Severe lesion	112.73 (9.95)	117.5	3	
VCUG – VUR grade				**0.923[a]**
0	108.6 (37.0)	100.3	8	
1	119.6 (16.70)	118.4	6	
2	74.4 (18.0)	68.1	3	
UDS – Bladder Pattern				**0.187**
Normal	87.53 (23.70)	86.1	4	
Incontinent	110.10 (38.12)	99.3	9	
High Risk	118.13 (12.30)	117.1	4	
UTI				0.365
No	91.20 (9.85)	90.7	3	
Yes	109.90 (33.70)	109.8	14	
Creatinine Clearance Stage				**0.652**
1	123.53 (24.32)	101.3	13	
2	116.87 (52.33)	111.1	4	
ACE 2 (µmol/min./mL)				
DMSA				**0.269**
44 to 40 %: Mild lesion	0.19 (0.15)	0.16	7	
39 to 35%: Moderate lesion	0.14 (0.16)	0.07	7	
34 to 30%: Severe lesion	0.17 (0.07)	0.2	3	
VCUG – VUR grade				**0.700[a]**
0	0.16 (0.14)	0.13	8	
1	0.16 (0.16)	0.08	6	
2	0.17 (0.10)	0.17	3	
UDS – Bladder Pattern				**0.040**
Normal	0.29* (0.14)	0.25	4	
Incontinent	0.15 (0.13)	0.1	9	
High Risk	0.07* (0.02)	0.07	4	
UTI			**0.097**	
No	0.28 (0.17)	0.20	3	
Yes	0.13 (0.12)	0.08	14	
Creatinine Clearance Stage			**0.391**	
1	0.18 (0.15)	0.10	13	
2	0.11 (0.06)	0.11	4	

continued

	Average (SD)	Median	n	p
Urynary ACE (mg/mL) /creatinine				
DMSA				**0.550**
44 to 40 %: Mild lesion	0.45 (0.26)	0.40	7	
39 to 35%: Moderate lesion	0.44 (0.15)	0.50	7	
34 to 30%: Severe lesion	0.63 (0.45)	0.60	3	
VCUG – VUR grade				**0.680**
0	0.52 (0.32)	0.35	8	
1	0.48 (0.21)	0.30	6	
2	0.36 (0.11)	0.55	3	
UDS – Bladder Pattern				**0.590**
Normal	0.42 (0.26)	0.35	4	
Incontinent	0.45 (0.29)	0.30	9	
High Risk	0.60 (0.14)	0.55	4	
UTI				**0.053**
No	0.76 (0.35)	0.80	3	
Yes	0.42 (0.19)	0.40	14	
Creatinine Clearance Stage				**0.080**
1	0.42 (0.18)	0.40	13	
2	0.67 (0.37)	0.70	4	

ACE = Angiotensin-Converting Enzyme 1; **ACE 2 =** Angiotensin-Converting Enzyme 2; **DMSA =** Dimercaptosuccinic Acid Scintigraphy; **UDS =** Urodynamic Study; **UTI =** Urinary Traction Infection; **VCUR =** Voiding Cystourethrogram; **VUR =** Vesicoureteral Reflux

* = Significant differences according to multiple Dunn-Bonferroni comparisons.

[a] = p = Descriptive level of the Kruskal-Wallis or Mann-Whitney test

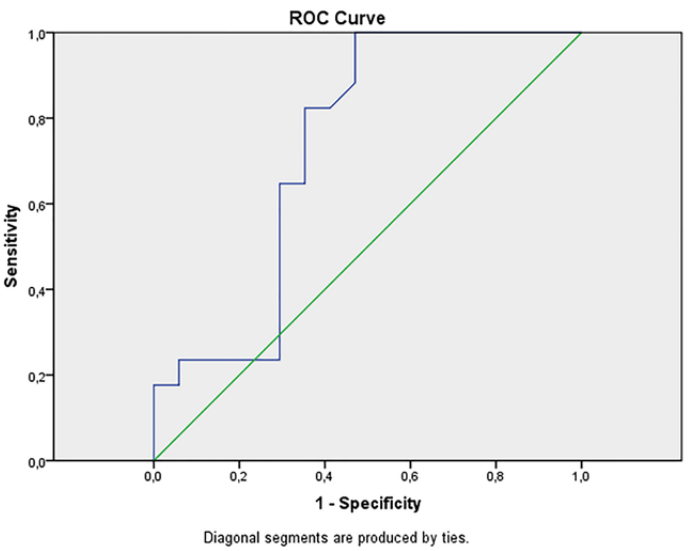
areas were observed in relation to ACE 2 and urinary ACE values between SG and CG (sensitivity and specificity).

DISCUSSION

In this study, it was observed that the vast majority of SG started their treatment in the first year of life (82.4%), but about half of them (47.1%) had their diagnosis only at birth. These results show us a prenatal pattern with some difficulties, since the intrauterine diagnosis of these patients would help both in terms of procedures and in the follow-up of these cases even earlier.

Only 3 of 17 children (17.6%) with abnormal DMSA started treatment after 1 year of life.

Figure 1 - ROC curve for serum ACE values in the Study and Control Groups.



Bauer in 2008 (12) observed that the institution of CIC and anticholinergic therapy in childhood revealed many advantages over time, as it leads to the prevention of the development of renal damage, as well as allows the patient autonomy in relation to its treatment. In a paper conducted by Elzeneini et al. (14), the authors observed that the performance of CIC in the first years of life is a prevention factor for renal damage, especially in women, which was not observed in this study, since of the 17 patients with altered DMSA, about 80% of the group consisted of women.

Lehnert et al. (15) and Humblet et al. (16) observed that patients who presented high detrusor pressure associated with low bladder emptying in urodynamic studies had renal damage and recurrent urinary tract infection with potential for the development of chronic renal disease and systemic arterial hypertension. In the study, about 75% of children with abnormal DMSA had urodynamic study abnormalities, with bladders associated with low bladder compliance or of high pressure, but with normal blood pressure levels.

Around up to one third of children with neurogenic bladder have VUR. (17, 18) VUR in these patients is usually secondary, and its main causes are associated with increased intravesical pressure (19, 20) and may also be secondary to recurrent urinary tract infections (which may cause weakening of the bladder valve mechanism), in addition to the dysfunctional urination process perpetuating the VUR in these patients (21). In this study, we observed the presence of VUR in about 50% of patients with renal injury diagnosed with DMSA, 23.5% of them with grade III and 17.7% with grades IV or V.

Follow-up of patients with MMC should be monitored by USRV, but in patients with obesity or scoliosis, DMSA should always be performed (22). The presence of renal scars increases the risk of hypertension and worsens renal injury. In this study, it was observed that the alteration of USRV was more evident in patients with altered DMSA (70.6%), with confirmed alteration of USRV in 94.1% of RG, while 47.1% of patients without altered DMSA also had altered USRV.

The renin-angiotensin-aldosterone system (RAAS) is currently one of the main involved in the mechanism of pressure reduction and renoprotection with several randomized controlled studies showing the reno-protective potential of angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II (ARB) in nephropathies of almost any etiology.

The optimal dose of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARA II) reduces albuminuria or proteinuria and decreases the development of

renal dysfunction more than placebo. However, there are no clinical evidences whether these strategies may influence long-term renal prognosis (23).

Recent studies suggest that urine protein composition could be a good information tool for pathogenic renal mechanisms, which would be of great importance in establishing the appropriate treatment for each pathophysiological mechanism (24-28). Despite the patients evaluated in this study already present renal damage detected in DMSA, there was no relationship between increased urinary ACE and altered creatinine clearance, nor its association with different stages of DMSA.

When relating serum ACE, ACE 2 and urinary ACE to radiological, urodynamic parameters and creatinine clearance stage, only ACE 2 was altered, with statistical significance when comparing the normal urodynamic study in relation to the high risk altered. However, this analysis was made in only 4 cases in each group and therefore, has a very limited value.

Despite advances in the understanding of RAAS as a participant in the mechanism of renal injury, the analysis of its serum (ACE and ACE 2) and urinary (urinary ACE) markers did not present significance in the diagnosis associated with the nephron-urological characteristics of patients with MMC and NB with renal injury previously detected by renal DMSA scintigraphy. We can conclude that only serum ACE was statistically significant to identify patients with renal injury. Nevertheless, it is worth remembering that the study sample had already departed from the diagnosis of renal injury by means of renal DMSA scintigraphy.

As limiting factors of the study we can highlight a small number of patients that prevents the generalization of the results. Data were obtained from a highly complex outpatient clinic in a tertiary sector, which may not represent the general patient population. On the other hand, as strengths of this research, the methodology used was standardized and the exams were evaluated by specialists. The patient's sample was homogeneous in relation to the clinical conditions and the control group was paired in accordance with gender and age.

CONCLUSIONS

Despite advances in the understanding of RAAS as a participant in the mechanism of renal injury, the analysis of its serum (ACE and ACE 2) and urinary (urinary ACE) markers were not significant in patients with MMC and BN with renal injury previously detected by renal DMSA scintigraphy.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Lloyd JC, Wiener JS, Gargollo PC, Inman BA, Ross SS, Routh JC. Contemporary epidemiological trends in complex congenital genitourinary anomalies. J Urol. 2013;190(4 Suppl):1590-5.
2. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol. 2010;88:1008-16.
3. Gobet R, Park JM, Nguyen HT, Chang B, Cisek LJ, Peters CA. Renal renin-angiotensin system dysregulation caused by partial bladder outlet obstruction in fetal sheep. Kidney Int. 1999;56:1654-61.
4. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920-4.
5. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82:445-53.
6. Ono CR, Sapienza MT, Machado BM, Pahl MMC, Liberato Jr W, Okamoto MRY. Padronização do método para cálculo da captação renal absoluta do 99mTC-DMSA em crianças. Radiol Bras. 2006; 39:33-8.
7. Fernbach SK, Maizels M, Conway JJ. Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol. 1993;23:478-80.
8. Tanaka H, Matsuda M, Moriya K, Mitsui T, Kitta T, Nonomura K. Ultrasonographic measurement of bladder wall thickness as a risk factor for upper urinary tract deterioration in children with myelodysplasia. J Urol. 2008;180:312-6; discussion 316.

9. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol. 1985;15:105-9.
10. Leal da Cruz M, Liguori R, Garrone G, Leslie B, Ottoni SL, Carvalheiro S, et al. Categorization of bladder dynamics and treatment after fetal myelomeningocele repair: first 50 cases prospectively assessed. J Urol. 2015;193(5 Suppl):1808-11.
11. Piquilloud Y, Reinharz A, Roth M. Studies on the angiotensin converting enzyme with different substrates. Biochim Biophys Acta. 1970;206:136-42.
12. Pedersen KB, Sriramula S, Chhabra KH, Xia H, Lazartigues E. Species-specific inhibitor sensitivity of angiotensin-converting enzyme 2 (ACE2) and its implication for ACE2 activity assays. Am J Physiol Regul Integr Comp Physiol. 2011;301:R1293-9.
13. Bauer SB. Neurogenic bladder: etiology and assessment. Pediatr Nephrol. 2008;23:541-51.
14. Elzeneini W, Waly R, Marshall D, Bailie A. Early start of clean intermittent catheterization versus expectant management in children with spina bifida. J Pediatr Surg. 2019;54:322-325.
15. Lehnert T, Weisser M, Till H, Rolle U. The effects of long-term medical treatment combined with clean intermittent catheterization in children with neurogenic detrusor overactivity. Int Urol Nephrol. 2012;44:335-41.
16. Humblet M, Verpoorten C, Christiaens MH, Hirche H, Jansen K, Buyse G, et al. Long-term outcome of intravesical oxybutynin in children with detrusor-sphincter dyssynergia: with special reference to age-dependent parameters. Neurourol Urodyn. 2015;34:336-42.
17. Brereton RJ, Narayanan R, Ratnatunga C. Ureteric re-implantation in the neuropathic bladder. Br J Surg. 1987;74:1107-10.
18. Sidi AA, Peng W, Gonzalez R. Vesicoureteral reflux in children with myelodysplasia: natural history and results of treatment. J Urol. 1986;136(1 Pt 2):329-31.
19. Koff SA. Relationship between dysfunctional voiding and reflux. J Urol. 1992;148(5 Pt 2):1703-5.
20. Seki N, Akazawa K, Senoh K, Kubo S, Tsunoda T, Kimoto Y, et al. An analysis of risk factors for upper urinary tract deterioration in patients with myelodysplasia. BJU Int. 1999;84:679-82.
21. Morioka A, Miyano T, Ando K, Yamataka T, Lane GJ. Management of vesicoureteral reflux secondary to neurogenic bladder. Pediatr Surg Int. 1998;13:584-6.
22. Shiroyanagi Y, Suzuki M, Matsuno D, Yamazaki Y. The significance of 99mtechnetium dimercapto-succinic acid renal scan in children with spina bifida during long-term followup. J Urol. 2009;181:2262-6; discussion 2266.
23. Rutkowski B, Tylicki L. Nephroprotective action of renin-angiotensin-aldosterone system blockade in chronic kidney disease patients: the landscape after ALTITUDE and VA NEPHRON-D trails. J Ren Nutr. 2015;25:194-200.
24. He W, Tan RJ, Li Y, Wang D, Nie J, Hou FF, et al. Matrix metalloproteinase-7 as a surrogate marker predicts renal Wnt/β-catenin activity in CKD. J Am Soc Nephrol. 2012;23:294-304.
25. Ju W, Nair V, Smith S, Zhu L, Shedden K, Song PXK, et al. Tissue transcriptome-driven identification of epidermal growth factor as a chronic kidney disease biomarker. Sci Transl Med. 2015;7:316ra193.
26. Kobori H, Harrison-Bernard LM, Navar LG. Urinary excretion of angiotensinogen reflects intrarenal angiotensinogen production. Kidney Int. 2002;61:579-85.
27. Viau A, El Karoui K, Laouari D, Burtin M, Nguyen C, Mori K, et al. Lipocalin 2 is essential for chronic kidney disease progression in mice and humans. J Clin Invest. 2010;120:4065-76.
28. Wada T, Furuichi K, Sakai N, Iwata Y, Yoshimoto K, Shimizu M, et al. Up-regulation of monocyte chemoattractant protein-1 in tubulointerstitial lesions of human diabetic nephropathy. Kidney Int. 2000;58:1492-9.

Correspondence address:
Marcela Leal da Cruz, MD
Departamento de Urologia,
Centro de Apoio à Criança com
Anomalia Urológica - CACAU
Rua Maestro Cardim, 560/215
01323-000 São Paulo, SP, Brasil
Fax: +55 11 3287-3954
E-mail: ma_celaleal@yahoo.com.br

SURGICAL TECHNIQUE

Vol. 46 (5): 814-821, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0101

Transition from open partial nephrectomy directly to robotic surgery: experience of a single surgeon to achieve "TRIFECTA"

Tiago Mendonça Lopez Castilho [1], Gustavo Caserta Lemos [1], Jonathan Doyun Cha [1], José Roberto Colombo [1], Oliver Rojas Claros [1], Maria Beatriz Lemos [1], Arie Carneiro [1]

[1] *Hospital Israelita Albert Einstein, São Paulo, SP, Brasil*

ABSTRACT

Introduction: Recent data suggest that robotic platform has become the most accessible minimal invasive surgery even for surgeons without previous training in laparoscopy. Laparoscopic partial nephrectomy (LPN) is a well-stablished procedure, however, with high level of complexity and long learning curve that limit its use.

Objective: To describe safety, efficiency and learning curve of a single surgeon without previous experience in LPN to reach "TRIFECTA" at robot-assisted partial nephrectomy (RAPN).

Patients and Methods: This is a retrospective study, with prospective data collection of 101 patients submitted to RAPN by a single surgeon. In order to analyze the learning curve, sample was chronologically divided in two phases: first phase: P1: 50 first patients, second phase: P2: 51 subsequent patients. TRIFECTA was defined as: ischemia time lower than 25 minutes, negative surgical margin and absence of severe complications (Clavien >2).

Results: Mean age of patients was 54 years (SD=11.85), median tumor size was 32mm (SD=17) and surgery was performed with zero ischemia time in 33.6% of patients (29.8% at P1 and 40.9% at P2). Demographic data of patients were similar between both groups, except tumor size (P1=27.5mm vs. P2=35.3mm; p=0.02) and body mass index (BMI) (P1=26.6kg/m^2 vs. P2=29kg/m^2; p=0.03). Rate of bleeding, surgical time, presence of positive margin and peri-operatory surgical complications were similar in both phases. TRIFECTA was higher in P2 in relation to P1 (P1: 58% vs. P2: 87.8%; p=0.002) and median time of hot ischemia was significantly lower at P2 (P1: 17.3 vs. P2: 11.7; p=0.02). At multivariate analysis independent factors related to TRIFECTA included: chronological phase (OR 10.74; 95% IC: 1.63-70.53; p=0.013) and tumor size (OR 0.95; 95% IC: 0.91-0.99; p=0.024).

Conclusion: RAPN seems to be safe and efficient with good functional and oncological results (TRIFECTA) since the beginning. Experience improvement was related to treatment of larger tumors, higher proportion of patients with zero ischemia and higher rate of TRIFECTA.

ARTICLE INFO

Tiago Mendonça L. Castilho
http://orcid.org/0000-0002-9500-0710

Keywords:
Kidney Neoplasms; Carcinoma, Renal Cell; Robotics; Nephrectomy

Int Braz J Urol. 2020; 46: 814-21

Submitted for publication:
May 14, 2019

Accepted after revision:
August 30, 2019

Published as Ahead of Print:
April 25, 2020

INTRODUCTION

Gold standard treatment of localized renal carcinoma is surgery, with oncologic and functional benefits very well stablished and validated (1, 2). Nephron-sparing surgery (NSS) is prefered and must always be performed whenever possible in the treatment of renal tumors (2). Most adequate access depends on the characteristics of the tumor and surgeon's experience (3).

Minimally invasive techniques have been more used in order to benefit patients with lower time of recovery, less pain and lower rate of complications related to surgical wound (4).

Many surgeons with basic training in laparoscopy are able to perform an ablative surgery such as radical nephrectomy with safety and good results. However, partial nephrectomy is a procedure with high complexity where it is mandatory to remove the tumor and to reconstruct renal parenchyma with hemostasis in a very short time interval. It is necessary the presence of a high trained team (3). The concept of TRIFECTA (negative surgical margins, ischemia time lower than 25 minutes and absence of severe complications) was described by Gill et al. and it is used to evaluate the surgical success of LPN (5, 6).

Transition from LPN to RAPN has been well studied (7). However, direct use of RAPN by surgeons without previous experience in LPN has not been well described in literature.

OBJECTIVE

To describe the safety, efficiency and learning curve of a single surgeon without previous experience in LPN of the first 100 cases treated by robot-assisted partial nephrectomy (RAPN).

Primary objective: to evaluate complication rate, time of hot ischemia (THI) and TRIFECTA rate.

Secondary objectives: to evaluate tumor size, complexity (nephrometry), surgical time, bleeding and rate of transfusion.

PATIENTS AND METHODS

Design of study, local, ethics

This is a retrospective study of data collected prospectively with a single arm of patients submitted to robot-assisted partial nephrectomy from January 2009 to June 2016, in a private hospital in Brazil by a single surgeon (GCL) without previous training in video-laparoscopy. The study was approved by the institutional ethics committee (76547917.5.0000.0071).

The data of the present study are presented in a descriptive form. In order to analyze the learning curve patients were divided chronologically in two groups, that were compared in all aspects. Sample was chronologically divided in two phases (first phase - P1=50 patients; second phase - P2=subsequent 51 patients).

Surgical technique

The procedure was standardized and performed according to previous study (3). Initially, all patients with high and intermediate complexity (RENAL score >6) were performed with clamping of renal artery. After the first 30 cases, well defined non-hilar nodules, with endophytic component of up to one centimeter were treated according to this standardization: renal hilum dissection isolating the renal artery and enucleation with clamping only if necessary.

Reconstruction of renal parenchyma was performed with two layers (medullary and cortical) with continuous suture (initially with Vycril® and posteriorly with V-loc suture). Early de-clamping (following medullary suture) was routinely performed after patient # 72.

Analyzed variables and outcomes

Abdominal computer tomography was reanalyzed by two urologists (TC, PPK) and the nodules were classified according to nephrometry R.E.N.A.L. score (8), and were considered with high complexity when score >6.

During the pre-operatory period, the following information were obtained: age, sex, body mass index (BMI), race, laterality, comorbidities, ASA (physicil status of the American Society of Anesthesiologists), renal function and tumor size. The tumors were classified as endophytic when more than 50% of its volume was located inside the renal parenchyma.

During surgery, the following data were collected: time of use of robot, bleeding (mL), complications, time of hot ischemia (THI), need of clamping, early de-clamping.

Following surgery, it was collected data related to serum hemoglobin (Hb), hematocrit (Ht), renal function and complications.

Complications were recorded and classified according to Clavien-Dindo system, and the

need of conversion to open surgery was classified as an adverse event (8).

Renal function of patients were evaluated by serum creatinine and creatinine clearance, calculated by the Cockroft-Gault formula. Evolution (or loss of renal function) was evaluated by an analysis in three moments: before surgery, recent post-operatory period (one to three months after surgery) and the last data during follow-up. Reduction of renal function was considered when creatinine clearance was lower than 80% of initial.

Surgical success (TRIFECTA) was defined, according to Gill et al., as: ischemia time lower than 25 minutes, negative surgical margin and absence of severe complications (Clavien>2) (4). If the patient did not meet all those criteria it was considered as unsuccessful.

Statistical Analysis

All statistical analysis were performed using the SPSS software for Windows version 20.0 (SPSS, Chicago, IL, USA). Significance level was <0.05.

Numeric variables were expressed as median and standard deviation. Non-parametric numeric variables were submitted to Mann-Whitney U test. In order to evaluate renal function in the three moments (related samples) it was used the Friedman paired test. For categorical variables, it was used the Chi-square test or exact of Fisher, depending on the quantity of positive at outcome (when expected values in contingence table cells were lower than 5). Multivariate analysis with binary logistic regression was performed to evaluate the factors related to TRIFECTA.

RESULTS

Median age of patients was 54 years (SD=11.85); median tumor size was 32mm (SD=17). Demographic characteristics of patients were similar between both phases except for the tumor size (P1:27.5mm vs. P2: 35.3mm; p=0.02) and body mass index (BMI) (P1:26.6 kg/m^2 vs. P2:29 kg/m^2; p=0.003) (Table-1).

Tumor complexity was similar between groups. However, in a sensitive analysis according to complexity level, it was observed that at P1 there was a higher proportion of patients with low complexity (70.3% vs. 60%, p=0.34) and a lower proportion of high complexity (8.1% vs. 12.5%, p=0.71); 79.1% at P1 were endophytic (more than 50% of tumor volume intraparenchymal) and 93.2% at P2 (p=0.056) (Table-1).

In a paired analysis of both phases it was not observed any difference of creatinine clearance before and after surgery (P1: 108.9 vs. P2: 109mL/min; p=0.987 and P1:125.2 vs. P2 126.8; p=0.775 (Table-2).

Mean ischemia time was significantly lower at P2 (P1: 17.3 vs. P2: 11.7 minutes; p=0.02) and the proportion of surgery with zero ischemia was proportionally lower at P1 (29.8% at P1 vs. 40.9% at P; p=0.259).

Bleeding, surgical time, presence of positive margin and peri-operatory complications were similar in both phases (Table-3).

Clavien 1 and 2 complications occurred in 16% of Phase 1 patients and in 7.8% of Phase 2 patients (p=0.506). Only one patient presented a severe complication at P1 (Clavien 3 or 4). This patient presented hematoma at the renal site that was treated with percutaneous drainage. One patient at P1 needed conversion to open surgery due to difficulty to expose the nodule (it was located at the posterior region of the upper pole of right kidney). Two patients showed positive margins (one identified at the intra-operatory freezing biopsy and the other with final diagnosis of oncocytoma where the margin was only identified at the pos-operatory anatomopathological exam). These patients are been followed, and showed no recurrence for 20 months. At P2 it was not observed any patient with severe complication or positive margin (Table-3).

Treatment success (TRIFECTA) was significantly higher at P2 in relation to P1 (P1: 58% vs. P2: 87.8%; p=0.002) (Table-3).

In the multivariate analysis, the independent factors related to TRIFECTA included: phase and tumor size (Table-4). Other analyzed aspects showed no correlation (BMI, pre-operatory creatinine, nephrometry and endophytic/exophytic localization).

DISCUSSION

This study shows the experience and evolution of a surgeon without previous experience in video-laparoscopy surgery, during the 100 first cases of RAPN. Since the beginning, the results were satisfactory, with significant improvement of TRIFECTA rate at the second phase (after 50 cases), especially due to the reduction of ischemia time. With experience gain, larger tumors were operated and the no-clamping technique was more used.

Table 1 - Demographic data.

	Phase 1		Phase 2		
		N		N	P
Age, median (SD)	55.4 (10.4)	50	53.8 (13.1)	51	0.49&
Male, %	80.00%	40	72.50%	37	0.37#
Female, %	20.00%	10	27.50%	14	
Bmi, median (SD)	26.6 (2.8)	42	29 (3.4)	28	0.003&
Laterality					0.51#
Right, %	38.30%	18	44.90%	22	
Left, %	61.70%	29	55.10%	27	
Renal score					0.62#
Low renal score, %	70.3%	26	60%	24	0.34#
Moderate renal score moderate, %	21.6%	8	27.5%	11	0.55#
High renal score, %	8.1%	3	12.5%	5	0.71$
Size, median (SD)	27.5 (12.6)	47	35.3 (19.5)	44	0.02&
ENDOPHITIC (>50% intraparenchymal), %	79.10%	41	93.2%	34	0.056#
Pre cr, medium (sd)	1.0 (0.3)	22	0.86 (0.2)	31	0.08&
Pre-op clearence, medium (SD)	103.7 (38.3)	19	120.2 (35)	27	0.13&
ASA 1 Classification	34.1%	15	32.7%	16	0.453#
ASA 2 Classification	63.6%	28	59.2%	29	
ASA 3 Classification	2.3%	1	8.2%	4	

= Chi-square test; **&** = Student t test; **$** = Fisher exact test

Table 2 - Paired analysis of clearance of creatinine.

	PHASE 1			PHASE 2		
		N	p		N	p
PRE-OP CLEARENCE PRE-OP, MEDIUM (SD)	109 (40.7)	16	0.987&	126.8 (37.4)	19	0.775&
POST-OP CLEARENCE, MEDIUM (SD)	108.9 (45.7)	16		125.2 (36.8)	19	

& = Paired t Student test

Table 3 - Peri-operatory data.

	PHASE 1		PHASE 2		
		N		N	P
Surgical time, medium (SD)	114.3 (29.7)	44	120 (48.5)	31	0.46&
Clamping time , medium (SD)	17.3 (13.1)	46	11.7 (10.9)	49	0.02&
Use of clamp					0.259#
With clamp	70.2%	33	58.1%	29	
Without clamp	29.8%	14	40.9%	20	
TRIFECTA 25 min. %	58%	29	87.8%	36	0.002#
Bleeding, medium (sd)	295.6 (372)	39	375.3 (282)	38	0.88&
Positive margin, %	2.3%	1	0	0	0.344#
Clavien 1/2, complication, %	16%	8	7.8%	4	0.506#
Clavien 3/4, complication %	2%	1	0	0	

#: \Chi-square test; **&:** Student t test

Table 4 - Multivariate logistic regression (outcome: to reach 25 min. Trifecta).

	OR (CI 95%)	P
PHASES	10.74 (1.63-70.53)	0.013
Size	0.95 (0.91-0.99)	0.024
BMI	0.94 (0.76-1.15)	0.572
Endo/Exophytic	0.07 (0.00-1.37)	0.080

The steep learning curve, of the transition from open partial nephrectomy to laparoscopy has become one of the most limiting factor for the use of minimally invasive techniques for this procedure, used only in a few centers with a big number of surgeries and specialized team. Robotic platform is proving to be an important tool to change paradigms, mainly in urologic surgery and has made minimally invasive surgery more available, even for surgeons without previous experience in video-laparoscopy (9, 10). This fact is related to the characteristics of this technology, that allows for a shortening of the learning curve, assuring the same functional and oncological results of conventional surgery (5, 11, 12).

With the advances of minimally invasive surgery, it is possible to reduce the hospitalization time and costs, not only of the surgery itself but the social costs, as described by the series of Chang et al. they demonstrated a medium withdrawal time of 35 days from work, from 7 to 92 days, with a medium salary loss of US$ 10.152 in the United States (13).

In the last years, a great number of institutions acquired the robotic platform, even in developing countries. Radical prostatectomy is the main surgery in most programs, and high volume surgeons, used to conventional surgery, are using it more frequently. The transition from radical prostatectomy to robot-assisted was widely

studied and the data showed that it is not necessary previous experience with laparoscopic radical prostatectomy (14).

Ghani et al. reported an expressive increase of the use of robotic platform instead of laparoscopic surgery in partial nephrectomy in the US. It was also suggested that it is possible to move from open surgery to robot-assisted without learning video-laparoscopy (9) and the number of urologists that are using minimally invasive technique is increasing. This fact was also observed in our institution where the robotic platform allowed for a wider access to minimally invasive procedure.

The promising results of our study since the first patients may be explained by the adoption of a structured program with PROCTOR to follow the procedures until consolidation of learning of surgeons, allowing for a safe and efficient transition from conventional technique to robot-assisted.

Many surgeons, especially those from developing countries, have limited training in laparoscopy and use open conventional surgery routinely, particularly in more complex cases. With the dissemination of the robotic platform and wider availability, more and more surgeons without previous training in laparoscopy are been trained to use the robotic platform (15).

The rate of conversion to open surgery, complications and positive margins are closely related to the experience of the surgeon. Similar to our study, Khalifeh et al. also reported conversion from open surgery at first phase, with absence of any type of complications, positive margins and ischemia time longer than 25 minutes, for partial nephrectomy (16). Similarly, Haber et al. (12) reported all conversions at the first 20 patients.

Hot ischemia time has already been widely studied and it was stablished that the lower the time the better the functional preservation (17). However, the ideal and safe limit is still being debated. Originally, the time of 30 minutes was considered the limit time for preservation of the renal parenchyma (18), but this value has been reduced along time. The most used concept in several studies and in our series was proposed by Gill et al. that stablished a goal of time lower than 25 minutes (4). Medium time of hot ischemia in our series was 22 minutes. We observed a significant reduction of ischemia time (p=0.034) when we compared P1 and P2 patients; however, since the first cases, we have observed "ideal" times compared to international series (19). Gill et al. reported a lowering of the medium time of hot ischemia from 32 to 14 minutes only after 500 patients operated (4). Our initial results probably were superior than those described by Gill due to the model of implantation of the program. Our program had a PROCTOR in all procedures to ensure standardization, quality and safety since the first cases.

In our series, at P2 there was an important change of ischemia results, that certainly was reflected in the TRIFECTA results. This occurred mainly due to change of approach and more frequent use of no-clamping technique and early de-clamping, that certainly was the main factor related to the increase of TRIFECTA at Phase 2. Different from others authors, we observed a significant reduction of the ischemia time due to a wider use of the no-clamping technique and not due to lower time of suture (17): more important than agility, experience made us confident to change our approach and to perform a high quality surgery even with more bleeding.

At P2 we observed a higher rate of bleeding and this may also be justified by the increased use of the no-clamping technique. However, this difference had no clinical significance and did not alter the rate of transfusion.

Rate of complications at literature varied from 8% to 22% (20, 21) and in our was 5.88% with no Clavien 3 or 4 at P2.

In relation to oncological results, we observed positive margins in two patients, exclusively at P1. According to good practices of oncologic surgery, it is essential to assure negative margins. Otherwise, at literature it was not possible to demonstrate an increased risk of local recurrence or progression to metastatic disease in patients submitted to partial nephrectomy with positive margins (22). Recent studies investigated the impact of the presence of microscopic positive surgical margins that suggested that their presence was not related necessarily to residual disease (23, 24). Therefore, according to current scientific knowl-

edge, the presence of positive surgical margin at post-operatory of partial nephrectomy is still being highly debated, and should not be used as the only or the main indicator of efficiency of oncologic surgery (25).

Differently of other series, such as Carneiro et al., that demonstrated a significant increase of renal complexity and size of tumor, as well as endophytic cases in later groups (7), in our study we have not identified any difference of nephrometry between the two phases, except by the tumor size, where it was observed an increase at P2 as well as more endophytic cases.

At Gill et al. series, evaluation of progression of renal function in three different moments in the same patient showed in the last patients submitted to laparoscopic partial nephrectomies a lowering of medium glomerular filtration rate (GFR) of 11% (4). In our series, there were no significant alterations of GFR regardless the moment, demonstrating the safety of functional preservation (Table-1).

Similar to the study of Khalifeh et al., TRIFECTA rate above 60% was reached in special after the first 50 patients, similar to other studies, that reported a short and safe learning curve (16, 26). We considered our results favorable to acquisition of a learning curve without compromising the final results; however, we agree that it is necessary more 30 or 40 cases to reach stable and consistent results and mastering the technique (16, 26). And as quoted by Larcher et al., after 150 patients it is not observed any additional improvement of ischemia time (27).

At multivariate analysis, the independent factors of TRIFECTA included the experience of the surgeon and the size of the tumor. Therefore, we suggest that in the beginning of the learning curve tumors with lower volume and lower nephrometry must be selected, although in the last aspect in our series that fact was not observed.

It is important to highlight that this study has some limitations. This is a small series with a short follow-up period compared to some already published in big centers of developed countries.

CONCLUSIONS

This study demonstrated that the transition from open nephrectomy to robot-assisted without learning laparoscopic nephrectomy is safe, with satisfactory functional and oncologic results since the beginning (TRIFECTA). Increased experience lead to a higher proportion of patients operated with zero ischemia and TRIFECTA.

ABBREVIATIONS

LPN = laparoscopic partial nephrectomy
RAPN = robot-assisted partial nephrectomy
BMI = body mass index
NSS = nephron sparing surgery
IT = ischemia time
HIT = hot ischemia time
Hb = Serum Hemoglobin
Ht = Hematocrit
GFR = Glomerular filtration rate
ASA = Classification of physical status of the "American Society of Anesthesiologists"

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, Faraday MM, et al. Guideline for management of the clinical T1 renal mass. J Urol. 2009;182:1271-9.
2. Van Poppel H, Becker F, Cadeddu JA, Gill IS, Janetschek G, Jewett MA, et al. Treatment of localised renal cell carcinoma. Eur Urol. 2011;60:662-72.
3. Lemos GC, Apezzato M, Borges LL, Colombo JR Jr. Robotic-assisted partial Nephrectomy: initial experience in South America. Int Braz J Urol. 2011;37:461-7.
4. Gill IS, Kamoi K, Aron M, Desai MM. 800 Laparoscopic partial nephrectomies: a single surgeon series. J Urol. 2010;183:34-41.
5. Hung AJ, Cai J, Simmons MN, Gill IS. "Trifecta" in partial nephrectomy. J Urol. 2013;189:36-42.
6. Mottrie A, De Naeyer G, Schatteman P, Carpentier P, Sangalli M, Ficarra V. Impact of the learning curve on perioperative outcomes in patients who underwent robotic partial nephrectomy for parenchymal renal tumours. Eur Urol. 2010;58:127-32.
7. Carneiro A, Sivaraman A, Sanchez-Salas R, Di Trapani E, Barret E, Rozet F, et al. Evolution from laparoscopic to robotic nephron sparing surgery: a high-volume laparoscopic center experience on achieving 'trifecta' outcomes. World J Urol. 2015;33:2039-44.

8. Patel MN, Krane LS, Bhandari A, Laungani RG, Shrivastava A, Siddiqui SA, et al. Robotic partial nephrectomy for renal tumors larger than 4 cm. Eur Urol. 2010;57:310-6.
9. Ghani KR, Sukumar S, Sammon JD, Rogers CG, Trinh QD, Menon M. Practice patterns and outcomes of open and minimally invasive partial nephrectomy since the introduction of robotic partial nephrectomy: results from the nationwide inpatient sample. J Urol. 2014;191:907-12.
10. Patel MN, Bhandari M, Menon M, Rogers CG. Robotic-assisted partial nephrectomy. BJU Int. 2009;103:1296-311.
11. Aboumarzouk OM, Stein RJ, Eyraud R, Haber GP, Chlosta PL, Somani BK, et al. Robotic versus laparoscopic partial nephrectomy: a systematic review and meta-analysis. Eur Urol. 2012;62:1023-33.
12. Haber GP, White WM, Crouzet S, White MA, Forest S, Autorino R, et al. Robotic versus laparoscopic partial nephrectomy: single-surgeon matched cohort study of 150 patients. Urology. 2010;76:754-8.
13. Chang P, Renehan P, Taylor KN, Dewey LE, McAnally KC, Hyde S, et al. Societal costs of localized renal cancer surgery. Can J Urol. 2018;25:9401-6.
14. Ahlering TE, Skarecky D, Lee D, Clayman RV. Successful transfer of open surgical skills to a laparoscopic environment using a robotic interface: initial experience with laparoscopic radical prostatectomy. J Urol. 2003;170:1738-41.
15. Kural AR, Atug F, Tufek I, Akpinar H. Robot-assisted partial nephrectomy versus laparoscopic partial nephrectomy: comparison of outcomes. J Endourol. 2009;23:1491-7.
16. Khalifeh A, Autorino R, Hillyer SP, Laydner H, Eyraud R, Panumatrassamee K, et al. Comparative outcomes and assessment of trifecta in 500 robotic and laparoscopic partial nephrectomy cases: a single surgeon experience. J Urol. 2013;189:1236-42.
17. Faria EF, Caputo PA, Wood CG, Karam JA, Nogueras-González GM, Matin SF. Robotic partial nephrectomy shortens warm ischemia time, reducing suturing time kinetic even for an experienced laparoscopic surgeon: a comparative analysis. World J Urol. 2014;32:265-71.
18. Gettman MT, Blute ML, Chow GK, Neururer R, Bartsch G, Peschel R. Robotic-assisted laparoscopic partial nephrectomy: technique and initial clinical experience with DaVinci robotic system. Urology. 2004;64:914-8.
19. Baumert H, Ballaro A, Shah N, Mansouri D, Zafar N, Molinié V, et al. Reducing warm ischaemia time during laparoscopic partial nephrectomy: a prospective comparison of two renal closure techniques. Eur Urol. 2007;52:1164-9.
20. Dulabon LM, Kaouk JH, Haber GP, Berkman DS, Rogers CG, Petros F, et al. Multi-institutional analysis of robotic partial nephrectomy for hilar versus nonhilar lesions in 446 consecutive cases. Eur Urol. 2011;59:325-30.
21. Gupta GN, Boris R, Chung P, Linehan WM, Pinto PA, Bratslavsky G. Robot-assisted laparoscopic partial nephrectomy for tumors greater than 4 cm and high nephrometry score: feasibility, renal functional, and oncological outcomes with minimum 1 year follow-up. Urol Oncol. 2013;31:51-6.
22. Permpongkosol S, Colombo JR Jr, Gill IS, Kavoussi LR. Positive surgical parenchymal margin after laparoscopic partial nephrectomy for renal cell carcinoma: oncological outcomes. J Urol. 2006;176(6 Pt 1):2401-4.
23. Breda A, Stepanian SV, Liao J, Lam JS, Guazzoni G, Stifelman M, et al. Positive margins in laparoscopic partial nephrectomy in 855 cases: a multi-institutional survey from the United States and Europe. J Urol. 2007;178:47-50.
24. Gill IS, Matin SF, Desai MM, Kaouk JH, Steinberg A, Mascha E, et al. Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. J Urol. 2003;170:64-8.
25. Yossepowitch O, Thompson RH, Leibovich BC, Eggener SE, Pettus JA, Kwon ED, et al. Positive surgical margins at partial nephrectomy: predictors and oncological outcomes. J Urol. 2008;179:2158-63.
26. Pierorazio PM, Patel HD, Feng T, Yohannan J, Hyams ES, Allaf ME. Robotic-assisted versus traditional laparoscopic partial nephrectomy: comparison of outcomes and evaluation of learning curve. Urology. 2011;78:813-9.
27. Larcher A, Muttin F, Peyronnet B, De Naeyer G, Khene ZE, Dell'Oglio P, et al. The Learning Curve for Robot-assisted Partial Nephrectomy: Impact of Surgical Experience on Perioperative Outcomes. Eur Urol. 2019;75:253-6.

Correspondence address:
Arie Carneiro, MD
Hospital Israelita Albert Einstein
Av. Albert Einstein, 627, Bloco A1, Sala 303
Telephone: + 55 11 2151-2303
E-mail: arie.carneiro@ein

EXPERT OPINION

Vol. 46 (5): 822-824, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.02

Quick beginners guide and tips on how to write a manuscript

Leonardo Oliveira Reis [1, 2]

[1] UroScience, Departamento de Urologia, Universidade de Estadual de Campinas – Unicamp, Campinas, SP, Brasil; [2] Disciplina de Urologia, Pontifícia Universidade Católica de Campinas - PUC - Campinas, SP, Brasil

COMMENT

Do you have a piece of work that might be appreciated by many experts all over? Make sure it was Ethics Committee appreciated and just take a weekend of work and make a competitive manuscript, the very first step to get published.

If you really understand something, you must be able to explain it in an easy way, and that is our challenge when compiling experience on "how to write a manuscript" without overkilling yourself.

This guide will make possible to easily transform your "idea", study, thesis in a science "brick" or "cell" as we are more at the biological side, as the smallest structural and functional unit of the whole body of knowledge on every topic, accessible to other scientists all over the globe.

TO THE POINT

TITLE: Straight message that hooks the reader. Can be a disrupting question or even an answer. Be creative – it really matters.

ABSTRACT: a mini manuscript with the essentials in structured 250 words. It is easier to make it unstructured in case you need, than the opposite. Purpose/Methods/Results/Conclusions.

MANUSCRIPT OVERVIEW

In the Surgery/Urology field usually 3000 words is the rule, distributed in the percentages below:

INTRO: 10 % - 3 paragraphs right to the point – not a discussion, never longer.

METHODS: 20 - 30 % - may vary according to the methodology density/complexity.

RESULTS: 20 - 30 % - may vary according to results density/complexity.

DISCUSSION: 20 – 30 % - perspective related to the literature.

CONCLUSION: 1 paragraph, just a message, maybe the Discussion last paragraph.

MANUSCRIPT IN DETAIL

INTRODUCTION: 3 paragraphs (less is more – introduction is not a discussion).

Paragraph 1- Shows the issue relevance / impact – prevalence, morbidity, mortality.

Paragraph 2- Identifies the "GAP" or what is unknown (the study Justification).

Paragraph 3- Fills de "GAP", usually describes the study hypothesis/objectives.

METHODS: usually 6 to 9 paragraphs.

Like in a cake recipe the reader should be able to replicate your study. Describe in a chronological sequence, keep to the essential steps. Rely on previous papers and keep to brief descriptions. Everything you have before putting the plan in practice belongs to methods.

RESULTS: usually 6 to 9 paragraphs.

Everything you obtain after putting in practice what were planned belongs to results. Tables and figures illustrate the story (complement never repeat). A chronological description is usually adequate.

Initial results are usually those that characterize the environment, the cohort and is essential to define study representativeness and applicability, before showing what was found in fact (i.e. Table-1, demographics). Just show data – never discuss in the results section. If too much data, think about organizing in different scopes, making more than one paper.

DISCUSSION: usually 6-9 paragraphs.

Paragraph 1: Describe the message in your results. While in the RESULTS section you showed the numbers, tables, graphics, p values, etc.; you will now give it an interpretation, a description of what you found: what increased, decreased, kept stable? How strong/ big was it? Then develop the following:

How the study/results interact with what is already published? In which aspects it confirms (or which studies your data supports), confronts (which studies your data might refute) or adds to previous data/studies (in which aspects it is new)?

Last Paragraph: Recognize the study limitations and show clinical implications, future perspectives.

CONCLUSION: 1 Paragraph: Expand the title... to give your message. Obviously supported by your results only. Avoid overstatements (don't tell what was not showed/ supported by your results).

REFERENCES: Have read the best evidence available on the topic you are writing and keep the essential and UpToDate works as references. Avoid using review articles cause might bypass the real authors that built the "bricks" you might be using.

LAST WORDS

Keep the habit of reading papers, looking deep in their skeleton or structure and doesn't matter how much experience you have, just follow the above-mentioned steps and put your study or thesis in perspective. Usually less is more and every assumption you make must be substantiated by facts/data (1). Know that your audience is made of editors, reviewers, readers, scientists and remember, the main challenges in this game are to:

Write a clear, easy, informative and enjoyable text.

Be honest and transparent.

With that you will convince the editor and reviewers about the importance of your manuscript and hook the reader's attention with your published paper, elevating the chances of acting as one fundamental "brick" in the wilderness of scientific building.

In this enjoyable process you will perceive that paper structures vary with hyper- and hypotrophy segments and eventual "appendices" according to the strategy/methodology. When you become proficient in seeing the papers' skeleton through the "soup of words", is time to the next step, the quality control by using specific reporting guidelines, checklists and quality control according to the study type at <https://www.equator-network.org/> (2).

Good luck, respect others ideas, believe in yourself, and remember, beyond the academic arena resilience is one of the most important qualities.

FUNDING

"National Council for Scientific and Technological Development" – CNPq, Research Productivity: 304747/2018-1

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Caulley L, Catalá-López F, Whelan J, Khoury M, Ferraro J, Cheng W, et al. Reporting guidelines of health research studies are frequently used inappropriately. J Clin Epidemiol. 2020;122:87-94.
2. Enhancing the QUAlity and Transparency of health Research (EQUATOR). Available at. <https://www.equator-network.org/> accessed 05/11/2020

Leonardo Oliveira Reis, MD, PhD

Departamento de Urologia, Universidade de Estadual de Campinas - Unicamp, Campinas, SP, Brasil
Disciplina de Urologia, Pontifícia Universidade Católica de Campinas - PUC - Campinas, SP, Brasil
E-mail: reisleo.l@gmail.com

ARTICLE INFO

Reis LO
https://orcid.org/0000-0003-2092-414X

Int Braz J Urol. 2020; 46: 822-4

Submitted for publication:
May 05, 2020

Accepted:
May 15, 2020

EXPERT OPINION

Vol. 46 (5): 825-842, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.03

Primary penile Kaposi's sarcoma in HIV-seronegative patient: a case report and literature review

Gianmartin Cito [1], Roberto Di Costanzo [1], Simone Morselli [1], Andrea Cocci [1], Raffaella Santi [2], Gabriella Nesi [2], Alessandro Natali [1], Andrea Minervini [1], Marco Carini [1], Fabrizio Travaglini [1]

[1] Department of Urology, Careggi Hospital, University of Florence, Florence, Italy; [2] Pathology Section, Department of Health Sciences, University of Florence, Florence, Italy

INTRODUCTION

Background

Kaposi's Sarcoma (KS) is a reticuloendothelial system tumor, that may involve the skin, mucosa and viscera (1). It can be considered a malignant vasoformative neoplasia with endothelial proliferation and spindle cell formation on histologic examination. In recent years, there have been several changes in our understanding of KS, including its evolving epidemiology, pathogenesis, new clinical presentations and associations, descriptions of new histologic variants, and the emergence of novel biomarkers with promising targeted therapeutic agents (2). Despite these advances, KS remains the most prevalent malignancy among patients with acquired immune deficiency syndrome (AIDS), being related with drugs or transplant-associated immunosuppression. To our knowledge, this disease has a tight link to Human Herpesvirus 8 (HHV-8) infection, also known as KSHV (Kaposi Sarcoma-associated Herpes Virus). KS can occur in five different epidemiologic-clinical settings: AIDS-related (also known as epidemic), iatrogenic (iatrogenic immunodeficiency, such as that seen in organ transplant recipients), endemic (commonly in sub-Saharan Africa in individuals seronegative for human immunodeficiency virus, HIV), Classic (also known as sporadic KS) and MSM (man who have sex with man) without HIV infection, who are young or middle aged, not immunocompromised (3, 4). The epidemiology suggests that this cancer had an origin independent of HIV, as well as a directed search of DNA led to the discovery of KSHV involvement in the pathogenesis of KS (5). Actually, it is known that a combination of KSHV infection and impaired host immunity might be responsible for KS. However, although AIDSrelated KS and iatrogenic KS are associated with welldefined immunodeficiency, the impaired immune function in classic KS (related to 'immunosenescence', as an ageing immune system) and endemic KS (related to chronic infection and malnutrition) is not exactly characterized. In addition, KSHV can cause: I) two lymphoproliferative disorders, represented by the primary effusion lymphoma (PEL) (6) and the multicentric Castleman disease (MCD) (7), II) an inflammatory syndrome called KSHV inflammatory cytokine syndrome.

Whit regard to the clinical presentation, each recognized variant has different manifestations and different visceral involvement. It has been estimated that KS confined to the penis is uncommon and is more often observed in patients with AIDS (8), representing the first manifestation of KS in approximately 2 to 3% of HIV-positive patients. Otherwise, up to 20% of these patients may develop genital lesions in the course of the systemic disease (9, 10). Even more rare primary KS of the penis may be in case of HIV seronegative patients.

The aim of this study is to describe an uncommon clinical presentation of genital KS in HIV-seronegative man and to perform a narrative literature review of the cases described to date.

Epidemiology

KS, first described by Moritz Kaposi in 1,872, is a rare neoplasm that origins from the endovascular cells in a multifocal way-This enigmatic infrequent malignant disease has since received much resonance after the AIDS epidemic in the early 1980s, with an incidence of classic KS ranged from 0.01 per 100.000 personyears for the UK and 0.2 per 100.000 personyears for the USA. However, currently, the incidence of KS is reported to be 200-fold higher in recipients of solidorgan transplants, known as iatrogenic KS form, rather than in the general population (11). The incidence of KSHV in south Africa is very high, reaching >90% in some population, while in Europe prevalence is 20-30%, in Asia and USA is <10% (3). In the Early 1980s with the onset of AIDS emergency, one of the first sign was the rise of KSHV infections. Indeed, a rise of KS incidence of 20.000 time in general population and 300 times in AIDS patients was estimated compared to other immunosuppressed patients (12) with a higher rate for MSM (13). Moreover, with the introduction of combination antiretroviral therapy (cART) the incidence of AIDS related to KSHV decreased considerably (14).

Physiopathology

KSHV is a large double-stranded DNA herpesvirus with a protein covering by an icosahedral capsid, surrounded by tegument and enclosed in a lipid envelope derived in part from the cell membrane. Different glycoproteins in the viral envelope interact with celltypespecific cellular entry receptors such as integrins (including α3β1, αVβ5 and αVβ3), the cystine-glutamate transporter xCT, heparan sulfate and the tyrosine protein kinase receptor EPHA2). KSHV can infect several different cell types, including endothelial cells, B cells, epithelial cells, dendritic cells, monocytes and fibroblasts. Once inside the cell and after uncoating the virus genome enter in the nucleus where enter in lantecy phase as episome and undergoes sporadic bouts of lytic reactivation (15). Virus can induce latency in human B cells and endothelial cells, as others Herpes virus. During the latent state expresses the latency locus, which includes ORF71 (who encoding viral inhibitory protein vFLIP), ORF72 (encoding vCyclin), ORF73 (encoding latency-associated nuclear protein (LANA)), ORFK12 (encoding the kaposins, which are signalling proteins) and several microRNAs (miRNAs) (16, 17). The latent genes expressed can promote tumorigenesis supporting the survival of the infected cell. Indeed, vFLIP protein activates I κB kinase 1 (IKK1) to stimulate the nuclear factor κB (NFκB) pathway to increase cell survival, viral miRNAs inhibit apoptosis. Finally, miRNAs also promote endothelial cell reprogramming, and induces the migration and invasion of endothelial cells and vFLIP promotes vascular proliferation. The reactivation from the latency is determined by different stimuli that are not well defined. During this phase, the virus induces, at first the expression of Immediate early (IE) genes than, Delayed early (DE) genes. Similar to the protein products of latency genes, the protein products of lytic genes can contribute to tumorigenesis. The products of those genes (such as vIL6) can induce proinflammatory and angiogenic factors, including vascular endothelial growth factor (VEGF) and plateletderived growth factor (PDGF) (18, 19). In order to survive and to induce cell survival and cell proliferation, KSHV modulate many host cell signaling pathways, including the phosphoinositide 3kinase (PI3K)-AKT--mTOR pathway, the mitogenactivated protein kinase (MAPK) pathway and the NFκB pathway. KSHV encode also genes with the capacity to inhibit host immune respond. K3 and K5 are lytic genes that encode modulator of immune recognition 1 (MIR1) and MIR2 both of which inhibit major histocompatibility complex (MHC) class I antigen presentation to prevent the immune system. KSHV homologues of interferon regulatory factors (IRFs), viral IRFs (vIRFs), are lytic proteins that inhibit type I interferons. KSHV also encodes three CCchemokine ligands (CCLs, formerly known as vMIPs): vCCL1 (encoded by ORFK6), vCCL2 (encoded by ORFK4) and vCCL3 (encoded by ORFK4.1), which can negatively regulate in-

flammation. Finally, the KSHV K14 gene encodes for a viral OX2 (vOX2), an immunoglobulin superfamily member with homology to the cellular OX2 membrane glycoprotein (OX2, also known as CD200) that binds to the receptor CD200R and suppressed neutrophil activation, decreased CCL2 (also known as MCP1) and IL8 production and inhibited oxidative burst in neutrophils stimulated to undergo phagocytosis.

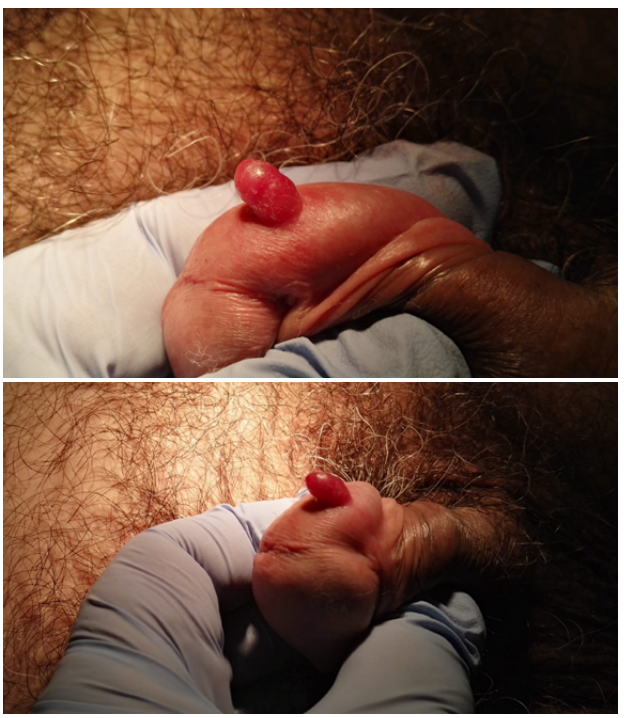
Clinical presentation

The behavior of the disease varies from a singular lesion localized in the skin, to a fleeting extensive respiratory and gastrointestinal visceral involvement. All variants of KS cutaneous lesions usually present as multiple, pigmented, raised or flat, painless that do not blanch. Classic variant (also known as sporadic KS) is typically confined to lower limbs with few lesions. Visceral and mucosal disease is rare and usually occurs in the gastrointestinal tract. Endemic is a typical manifestation of African children often present with multiple lymph nodes with lymphoedema and a very aggressive natural history of the disease, including visceral disease. AIDS-related is characterized by multiple cutaneous lesions on the limbs, trunk and face. Mucosal lesions, such as oral lesion, are common (identified in 20% of patients) and visceral involvement is seen in 15% of patients. Related with Iatrogenic immunodeficiency, such as in organ transplantation. Often presents as cutaneous KS lesions but both mucosal and, rarely, visceral disease can occur. Finally, in MSM patients the clinical manifestations included lesions that can occur at any skin sites, usually few. Visceral and mucosal disease is rare (3). Regarding visceral involvement, organ lesions are uncommon (in one study, only 15% of 469 patients had visceral lesions upon diagnosis with AIDSrelated KS) (20). Gastrointestinal and pulmonary lesions are more present in AIDS-related KS. Pulmonary lesions present with dyspnea, dry cough and sometimes hemoptysis, with or without fever, are lifethreatening. These lesions typically appear as a diffuse reticule nodular infiltrate and/or pleural effusion on chest radiography. Gastrointestinal lesions are usually asymptomatic, but may bleed or cause obstruction, and their presence is usually confirmed at endoscopy. However, CT scans, bronchoscopy and endoscopy are not warranted in patients unless they present symptoms indicative of visceral lesions (3). When there is clinical suspicion of KS, a biopsy sample is taken to confirm the diagnosis histologically. Pathologic diagnosis can often be made using conventional hematoxylin and eosin (H&E) and it shows some characteristic features such as, vascular proliferation in the dermis, an increased number of vessels without an endothelial cell lining, the presence of extravasated blood, spindle cells express endothelial markers and are considered to be the KS tumor cell (CD34, LYVE1 and VEGF receptor 3) (3). As concerned the therapy in patients with forms of KS when immunosuppression is potentially reversible, the firstline approach is to bolster the immune system. IFNα and alitretinoin (a retinoid panagonist receptor), are approved for AIDSrelated KS, as KSHV directed therapy (3). Otherwise, regarding the management of genital KS, no specific therapy has been described to date.

CASE DESCRIPTION

A 71-year-old heterosexual, Caucasian man, referred to our department for the presence of penile neoformation appeared from at least 6 months. At the clinical examination, a 0.6mm x 0.6mm x 0.3mm red painless radish nodule hemangioma-like was found on the gland near the frenulum (Figures 1A and 1B). He did not complain penile bother nor there were palpable inguinal lymph nodes. His past medical history reveled only hypertension and hyperuricemia under treatment. The urine analysis and blood laboratory tests showed normal results. The urine culture was negative for Neisseria Gonorrhoeae, Trichomonas Vaginalis, Ureaplasma Urealitycum, Mycoplasma hominis, Mycoplasma Genitalium, Clamydia Trachomatis. The enzyme-linked immunoassorbant assay (ELISA) sierology was negative for Troponema pallidum and HIV 1-2 infections. A complete surgical excisional biopsy of the lesion

Figures 1 A and B - Red painless radish nodule hemangioma-like on the gland near the frenulum.



was performed, with margin control (Figure-2). The histopathological examination showed a dermal tumor constituted by intersecting fascicles of spindle cells, arranged around slit-like vascular spaces admixed with numerous extravasated red blood cells and scattered inflammatory cells. The immunohistochemical staining evidences for HHV-8 both in the stromal cells and in the endothelial ones. In addition, the spindle cells were positively stained for CD31, CD34, and negatively for AE1, AE3, CITO-B, P63, ACTINA A4. These clinical and histopathological findings were compatible with a typical KS variant. Therefore, computed tomography (CT) of the abdomen and chest was scheduled, not showing any visceral involvement. The 3-months follow-up visit demonstrated the complete remission of the pathology without recurrences (Figure-3).

DISCUSSION

Literature review

An English-language literature research

Figure 2 - Penile biopsy showed a dermal tumor constituted by intersecting fascicles of spindle cells, arranged around slit-like vascular spaces admixed with numerous extravasated red blood cells and scattered inflammatory cells (A). At higher magnification, spindle cells exhibited mild to moderate atypia (B). Neoplastic cells stained positively for CD34 (C) and HHV-8 (D).

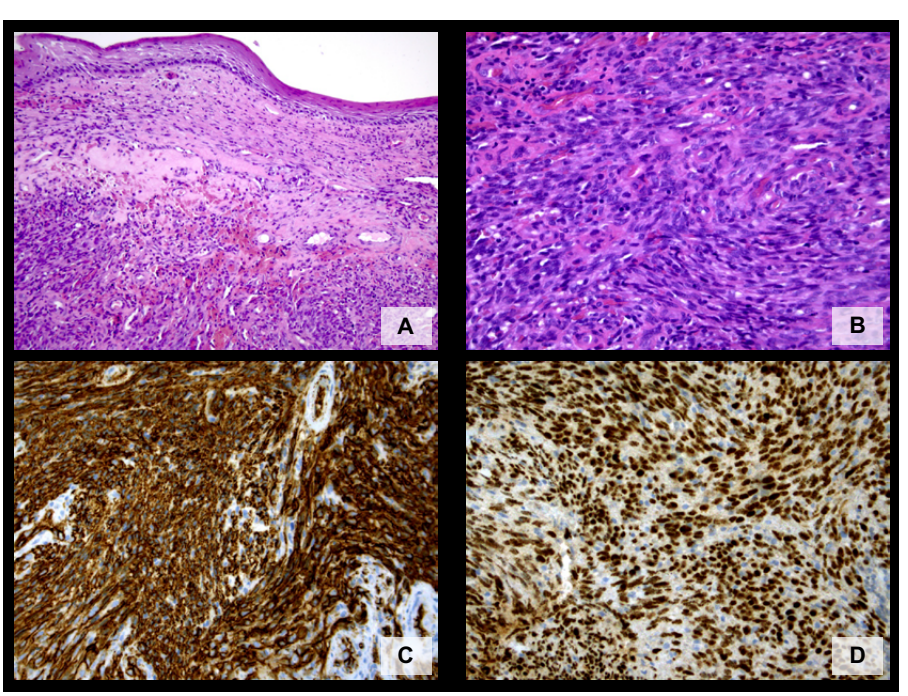
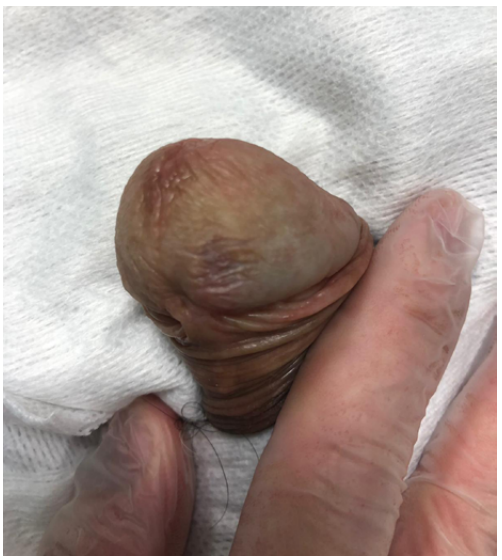


Figure 3 - Clinical examination revealed the complete remission of the pathology.



was conducted, focusing on the cases of penile KS in HIV positive and negative patients (Table-1). Two different authors (GC. and R. DC.) independently searched Medline, Scopus and PubMed databases using a single query in order to identify all the previous reports describing the diagnosis, clinical presentation, histological findings, therapy and recurrence rate of penile KS. The following terms were included: ((penile) OR penis) AND Kaposi's sarcoma) AND HIV. Finally, considering the period from 1985 to date, a total of 33 KS cases associated with KSHV, with penis as the only manifestation site of the disease, were found in literature. KS usually affects patients between the fifth and eighth decade of life living on the Mediterranean coastal areas where the HHV-8 infection is widespread. In the KS cases found in literature, patient's average age was 55.7 years (range 26-78 years). As showed by epidemiological evidences that highlight the strong link between the disease pathogenesis and HHV-8 infection, most of the patients with penile KS resulted positive for serology HHV-8 research. Equally, the histopathological examination found typical features of KS (Table-2). Since it was described a high HHV-8 sero-prevalence in individuals with high risk sexual activity, including homosexual, a focus on sexual behaviors are mandatory. However, according to our case, only few patients referred to have risk sexual intercourse (21-23). As concerned to the immunological status, three patients with isolated penile KS reported an immunosuppression HIV related (23, 24). The lesions described are definitely variable for manifestation, (nodule (23, 25-39), papular (22, 34, 40-44), ulcerated (27, 39, 45), granulomatous (21), verrucous (46) dimension 0-5mm (24, 31-33, 35, 40, 42, 43, 47), >6mm (21, 26, 28, 30, 34, 36, 37, 40-42,46), site (gland (21-23, 25, 26, 28-45, 48), coronal sulcus (22, 26, 29, 37, 40, 44, 45), prepuce (24, 47, 49), penilshaft (27, 46, 48), scrotum (23), frenulum (30)), color (reddish (23, 25-27, 29, 32, 34, 36, 40, 44, 45, 49), purplish (23, 29, 30, 33, 39, 41, 42, 43,), bluish (30, 42), skin colored (24), dark brown (48), number (single (26-28, 30-33, 35, 36, 38, 39, 41-43, 45, 47, 49) to multiple (21-25, 29, 34, 37, 40, 44, 46, 48,) and symptomatology (asymptomatic, painfull (45)). The most frequently involved site is the glans, sometimes in associations with swelling and lymphatic edema due to massive involvement and the most common manifestation is a nodular reddish or purplish lesion, single or multiple, sometimes ulcerated too. Lesions may also involve the foreskin, the coronal sulcus, or the meatus. In this last case urinary obstructive symptoms may occur. The involvement of the shaft is rare, usually being related to lesions located on the glans or coronal sulcus. Notably, the lesion observed in our patient was a single red radish pedunculated hemangioma-like lesion of the gland next to the frenulum. To our knowledge, this atypical clinical presentation is similar to others described in literature. Indeed, other comparable lesions described in literature varied from a red purple nodule, or radish 5mm papule in diameter of gland to a 1mm nodule next of the meatus. Nevertheless, it remains a rather infrequent manifestation because of its appearance, that could simulate a benign pedunculated lesion of vessels. According to other cases in literature, our case refers to an immunocompetent HIV-seronegative patient. Therefore, similar cases although rare, could not be infrequent. However, the management of

Table 1 - Data of patients with Kaposi's Sarcoma.

REFERENCE	PATIENT AGE	SEXUAL RISK	IMMUNODEPRESSION	HIV+	HHV	CLINICAL FEATURES
Case of classic Kaposi sarcoma of the penis successfully treated with radiotherapy. Kuriyama, et al. (21)	65	NO	NO	NO	HHV-8	asymptomatic reddish nodules on the glans penis
Kaposi's sarcoma: An unusual penile lesion in a HIV negative patient. De Rose, et al. (22)	75	NO	NO	NO	HHV-8	painful ulcerated red lesion on the glans that stretched from the urethral meatus to the coronal skin
Topical imiquimod 5% as a treatment for localized genital Kaposi's sarcoma in an HIV-negative man: a case report. Fairley, et al. (23)	43	YES	NO	NO	HHV-8	two fleshy granulomatous lesions on the glans and corona of the penis, 5–6 mm in diameter
Penile Kaposi's sarcoma in a HIV negative HHV-8 positive man. Kampantais, et al. (24)	50	NO	NO	NO	HHV-8	0,5 cm in size on the inner layer of the prepuce
Isolated penile Kaposi's sarcoma in a HIV-positive patient stable on treatment for three years. Lebari, et al. (25)	40	NO	YES	YES	HHV-8	two skin-coloured KS lesions on the prepuce of the penis, 5mm in diameter on the inner layer of the prepuce
Kaposi Sarcoma of the Penis in an HIV-Negative Patient. Cecchi, et al. (26)	52	NO	NO	NO	IgG NEGATIVE PER HHV-8	translucent, domeshaped, reddish nodule on the glans penis near the coronal sulcus. 8 mm in diameter
Primary Kaposi Sarcoma of Penis in HIV Negative Patient. Karami, et al. (27)	47	YES	NO	NO	HHV-8	papular indurate glandular and subcoronal multiple lesions
Kaposi's Sarcoma of the Penis as an Initial Urological Manifestation of AIDS A Report of Two Cases. Angulo, et al. (28)	28	YES	YES	YES	HHV-8	growing red-purple nodule on his glans penis

Kaposi's Sarcoma of the Penis as an Initial Urological Manifestation of AIDS A Report of Two Cases. Angulo, et al. (28)	26	YES	YES	YES	HHV-8	multiple cutaneous lesions in the penis, scrotum, right calf and leg
Penile Kaposi's sarcomas in a circumcised and HIV-seronegative patient. Gonen, et al. (29)	55	NO	NO	NO	not use HHV-8 test on patient	two reddish papules,5 mm in diameter on coronal sulcus near the frenulum and 2 mm in diameter on the glans
Primary Classic Kaposi's Sarcoma of the Penis in an HIV-Negative Patient. Kim, et al. (30)	68	NO	NO	NO	HHV-8	ulcerated dark reddish nodule on the penile shaft
Isolated Kaposi Sarcoma in two HIV negative patients. Seleit, et al. (31)	34	NO	NO	NO	HHV-8	The nodule was (1x1 cm) in size, on the glans penis lateral to urethral meatus
Exclusive penile Kaposi's sarcoma: report of an HIV-negative man successfully treated with radiotherapy. Zargari, (32)	71	NO	NO	NO	HHV-8	oedematous penis with purplish macular lesions over the glans penis and a few reddish small nodules on the coronal sulcus
Kaposi sarcoma of the penis in an HIV-negative patient Sarcoma de Kaposi de pênis em paciente HIV negativo. Guevara, et al. (33)	48	NO	NO	NO	HHV-8	The lesion was a purple color papule over the glans near the urethral meatus, measuring approximately 1cm
Kaposi sarcoma limited to glans penis. Conger K, et al. (34)	67	N/A	N/A	N/A	N/A	Single purplish slightly raised nodule (Ø 10 mm) on the glans near the frenulum
Kaposi sarcoma limited to glans penis. Conger, et al. (34)	55	N/A	N/A	N/A	N/A	Single painless bluish wart-like lesion on the frenulum
Kaposi's sarcoma of penis. Maiche, et al. (35)	70	N/A	N/A	N/A	N/A	Single nodule (Ø 5 mm) on the glans; local swelling

Disseminated Kaposi's sarcoma that is not associated with acquired immunodeficiency syndrome in a bisexual man. Marquart, et al. (36)	44	N/A	N/A	NO	N/A	Single red-brown nodule (Ø 5 mm) on the glans
Kaposi's sarcoma of the conjunctiva. Jaimowich, et al. (37)	74	N/A	N/A	N/A	N/A	Single painless, firm, smooth and purple nodule (Ø 5 mm) on the glans near the meatus
Spontaneous healing of Kaposi's angiosarcoma of the penis. Casado, et al. (38)	77	N/A	N/A	N/A	N/A	Six red smooth papulo-nodules (Ø 3–7 mm) on the glans and inner aspect of the foreskin
Kaposi's sarcoma of the penis. Zambolin, et al. (39)	47	N/A	N/A	NO	N/A	Single brown pedunculate lesion on the inner aspect of the prepuce near the frenulum
Radiation therapy for classic Kaposi's sarcoma presenting only on the glans penis. Lands, et al. (40)	54	N/A	N/A	NO	N/A	Multiple blue-purple to brown macules and papules (Ø 2–6 mm) on the glans
Radiation therapy for classic Kaposi's sarcoma presenting only on the glans penis. Lands, et al. (40)	50	N/A	N/A	NO	N/A	Maroon linear growth (8 mm) on the glans
Kaposi sarcoma limited to the glans penis. Myslovaty, et al. (41)	70	N/A	N/A	NO	N/A	Single purplish, slightly raised nodule (Ø 5 mm) on the glans
Primary classic Kaposi's sarcoma of glans penis – appearance on magnetic resonance imaging. Guy, et al. (42)	69	N/A	N/A	NO	N/A	Single smooth reddish-violet nodule on the glans (Ø 15 mm)
Purplish penile papule as a presenting sign of Kaposi's sarcoma. Grunwald, et al. (43)	75	N/A	N/A	NO	N/A	Single, non-tender, purplish papule (Ø 5 mm) on the glans

Kaposi's sarcoma limited to the penis treated with cobalt-60 radiotherapy. Ruszczack, et al. (44)	78	N/A	N/A	NO	N/A	Multiple dome-shaped violaceous and crusted nodules (Ø 5–10 mm) on the glans, coronal sulcus and foreskin; massive oedema of distal shaft
Primary Kaposi's sarcoma of the glans penis. Koyuncuoglu, et al. (45)	52	N/A	N/A	NO	N/A	Single painless nodule on the glans
Adult genitourinary sarcomas: a report of seventeen cases and review of the literature. Berkmen, et al. (46)	55	N/A	N/A	N/A	N/A	Single purplish ulcerated nodule on the glans
Adult genitourinary sarcomas: a report of seventeen cases and review of the literature. Berkmen, et al. (46)	60	N/A	N/A	N/A	N/A	Single purplish ulcerated nodule on the glans
A case of classical Kaposi's sarcoma of the penis showing a good response to high energy pulsed carbon dioxide laser therapy. Chun, et al. (47)	54	N/A	N/A	NO	N/A	Multiple, dark-brownish plaques on the glans and shaft
Penile Kaposi's sarcoma preceded by chronic penile lymphoedema. Schwartz, et al. (48)	45	N/A	N/A	NO	N/A	Lymphoedema followed by onset of two verrucous lesions on the glans and on the ventral shaft (Ø 30 mm) 2.5 years later
Penile Kaposi's sarcoma in a human immunodeficiency virus-seronegative patient. Kavak, et al. (49)	43	N/A	N/A	NO	N/A	Two reddish and smooth papules (Ø 4 mm) on the glans and coronal sulcus

Table 2 - Treatment, histopathological findings and recurrence of patients with KS.

REFERENCE	HISTOLOGY	TREATMENT	RECURRANCE	RECURRENCE FEATURE	RECURRENCE THERAPY
Case of classic Kaposi sarcoma of the penis successfully treated with radiotherapy. Kuriyama, et al. (21)	slit-like spaces filled with red blood cells and extensive proliferation of spindle-shaped cells	4-MV X-ray radiotherapy, a total of 60 Gy.	NO	N/A	N/A
Kaposi's sarcoma: An unusual penile lesion in a HIV negative patient. De Rose, et al. (22)	groups of spindle cells, extravascular erythrocytes, and macrophages filled with hemosiderin	subtotal circumcision and a glans biopsy	NO	N/A	N/A
Topical imiquimod 5% as a treatment for localized genital Kaposi's sarcoma in an HIV-negative man: a case report. Fairley, et al. (23)	spindle-cell proliferation. High cellularity and mitoses. Vascular spaces and capillaries with some red blood cells entrapped between spindle cells	cryotherapy; At week 8 imiquimod 5% cream for a total of six weeks of treatment.	NO	N/A	N/A
Penile Kaposi's sarcoma in a HIV negative HHV-8 positive man. Kampantais, et al. (24)	classical Kaposi's sarcoma	excision	NO	N/A	N/A
Isolated penile Kaposi's sarcoma in a HIV-positive patient stable on treatment for three years. Lebari, et al. (25)	penile prepuce KS.	excision of the lesion	YES	new skin-coloured lesion at the frenulum of the glans penis, 6X6X3 mm	cryotherapy and 5% imiquimod + surgical excision biopsy

Kaposi Sarcoma of the Penis in an HIV-Negative Patient. Cecchi, et al. (26)	spindle-shaped cells intermingled with vascular slits with intra- and extravascular red blood cells	excision of the lesion	NO	N/A	N/A
Primary Kaposi Sarcoma of Penis in HIV Negative Patient. Karami, et al. (27)	N/A	NO	NO	N/A	N/A
Kaposi's Sarcoma of the Penis as an Initial Urological Manifestation of AIDS A Report of Two Cases. Angulo, et al. (28)	KS	NO	NO	N/A	N/A
Kaposi's Sarcoma of the Penis as an Initial Urological Manifestation of AIDS A Report of Two Cases. Angulo, et al. (28)	KS	NO	NO	N/A	N/A
Penile Kaposi's sarcomas in a circumcised and HIV-seronegative patient. Gonen, et al. (29)	vascular lesions with spindle cell proliferation and increased mitotic activity. Vascular clefts with blood elements. Atypical spindle cells are organized as interlacing bundles with extravascular erythrocytes scattered around	excision of the lesion	NO	N/A	N/A
Primary Classic Kaposi's Sarcoma of the Penis in an HIV-Negative Patient. Kim, et al. (30)	spindle cells scattered between collagen bundles and small vascular proliferation (CD31-cd34 +)	circumcision	NO	N/A	N/A

Isolated Kaposi Sarcoma in two HIV negative patients. Seleit, et al. (31)	Confirmatory immunohisto. chemical staining for CD 34 antibody was done and reve. aled positive staining for endothelial cells and malignant spindle shaped cells	excision	NO	N/A	N/A
Exclusive penile Kaposi's sarcoma: report of an HIV-negative man successfully treated with radiotherapy. Zargari, (32)	proliferation of spindle cells forming slit-like structures in the dermis, compatible with typical Kaposi's sarcoma	radiotherapy with 3000 rad fractionated in 10 consecutive days.	NO	N/A	N/A
Kaposi sarcoma of the penis in an HIV-negative patient Sarcoma de Kaposi de pênis em paciente HIV negativo. Guevara, et al. (33)	proliferation and fascicles of spindle cells associated with angiogenesis		N/A	N/A	N/A
Kaposi sarcoma limited to glans penis. Conger, et al. (34)	N/A	Local excision	YES	Onset of a new lesion on the toe after 1 year	N/A
Kaposi sarcoma limited to glans penis. Conger, et al. (34)	N/A	Local excision	NO	No recurrence after 5 years	N/A
Kaposi's sarcoma of penis. Maiche, et al. (35)	N/A	Local excision	YES	Local recurrence after 1.5 years; no further recurrences after 3 years	N/A

Disseminated Kaposi's sarcoma that is not associated with acquired immunodeficiency syndrome in a bisexual man. Marquart, et al. (36)	N/A	Local excision + IFN-ř	YES	Onset of three new lesions on the toe, the thigh and the knee after 2 years	N/A
Kaposi's sarcoma of the conjunctiva. Jaimowich, et al. (37)	N/A	Not performed	YES	Spontaneous regression of the primary lesion and onset of a new lesion on the back after 7 months; new lesions on both legs and in the conjunctiva after 1 year	N/A
Spontaneous healing of Kaposi's angiosarcoma of the penis. Casado, et al. (38)	N/A	Not performed	YES	Spontaneous regression of the primary lesions after 1 year; no recurrences after 1.5 years	N/A
Kaposi's sarcoma of the penis. Zambolin, et al. (39)	N/A	Circumcision	NO	No recurrences after 10 months	N/A
Radiation therapy for classic Kaposi's sarcoma presenting only on the glans penis. Lands, et al. (40)	N/A	Radiation therapy	NO	No recurrences after 1.5 months	N/A

Radiation therapy for classic Kaposi's sarcoma presenting only on the glans penis. Lands, et al. (40)	N/A	Radiation therapy	NO	N/A	N/A
Kaposi sarcoma limited to the glans penis. Myslovaty, et al. (41)	N/A	Local excision	NO	No recurrences after 6 months	N/A
Primary classic Kaposi's sarcoma of glans penis – appearance on magnetic resonance imaging. Guy, et al. (42)	N/A	Local excision	YES	Onset of new lesions on the lower extremities after 2 years	N/A
Purplish penile papule as a presenting sign of Kaposi's sarcoma. Grunwald, et al. (43)	N/A	Local excision	NO	No recurrence after 2 years	N/A
Kaposi's sarcoma limited to the penis treated with cobalt-60 radiotherapy. Ruszczack, et al. (44)	N/A	Radiation therapy	NO	N/A	N/A
Primary Kaposi's sarcoma of the glans penis. Koyuncuoglu, et al. (45)	N/A	Local excision	NO	N/A	N/A
Adult genitourinary sarcomas: a report of seventeen cases and review of the literature. Berkmen, et al. (46)	N/A	Local excision	YES	Onset of three new lesions on the shaft after 1 year	N/A

Adult genitourinary sarcomas: a report of seventeen cases and review of the literature. Berkmen, et al. (46)	N/A	Local excision + chemotherapy	YES	Persistence of slight oedema after 1 year	N/A
A case of classical Kaposi's sarcoma of the penis showing a good response to high energy pulsed carbon dioxide laser therapy. Chun, et al. (47)	N/A	CO2 laser therapy	YES	Onset of a new lesion on the dorsum of the left hand after 5 months	N/A
Penile Kaposi's sarcoma preceded by chronic penile lymphoedema. Schwartz, et al. (48)	N/A	Local excision + radiation therapy	N/A	N/A	N/A
Penile Kaposi's sarcoma in a human immunodeficiency virus-seronegative patient. Kavak, et al. (49)	N/A	Local excision	N/A	N/A	N/A

patients with KS should include: exams to exclude ongoing infectious diseases, assessment of patient's immunological status, histological analysis following surgical biopsy and visceral involvement evaluation through CT or ultrasounds, despite it is not necessary in asymptomatic patients, according to others studies (3). In our case, we managed it with complete surgical excision of the lesion, as described by other authors (24, 26, 28, 30, 31, 35, 36, 38-40, 43, 44, 47, 49), with a disease recurrence in five cases (24, 30, 31, 36, 39) from a period of about 1-2 years. Other approaches described in literature could include radiotherapy (25, 29, 37, 42), subtotal circumcision associated with biopsy (45), cryotherapy associated with 5% Imiquimod cream (21), excisional biopsy associated with IFNα (32), biopsy with chemotherapy (39), CO2 (48), biopsy with radiotherapy (46). Furthermore, in five cases no therapy was performed (22, 23, 33, 34), two of them for the spontaneous regression of the disease (33, 34). The clinical course of primary penile KS is variable and no standardized follow-up exists to

date. In general, local recurrences are rare if the primary tumor is completely removed. In one of them (33) the authors refer recurrence of a new penis lesion after seven months, then after one year two lesions on both legs and one on conjunctiva. Other cases of recurrences occurred for therapy with biopsy with IFNα (32) and with CO2 (48). Respect the management of recurrence, it was described only a recurrence after excisional biopsy (24) in which case it was treated with a new biopsy with radiotherapy, with no recurrence. In our patient, at 6-months from surgery there are no signs of disease progression, although it is a too short follow-up period.

CONCLUSION

New-onset apparently benign lesions of penis in immunocompetent patients, even in absence of risk factors for sexually transmitted diseases, should be always investigated, because it could represent the first manifestation of primary KS in which penis could be the only isolated clinical presentation. The surgical management could represent a good therapeutic option, leading to disease clinical resolution with no further recurrence, thus providing histological diagnosis.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Antman K, Chang Y. Kaposi's sarcoma. N Engl J Med. 2000;342:1027-38.
2. Pantanowitz L, Dezube BJ. Advances in the pathobiology and treatment of Kaposi sarcoma. Curr Opin Oncol. 2004;16:443-9.
3. Cesarman E, Damania B, Krown SE, Martin J, Bower M, Whitby D. Kaposi sarcoma. Nat Rev Dis Primers. 2019;5:9.
4. Friedman-Kien AE, Saltzman BR, Cao YZ, Nestor MS, Mirabile M, Li JJ, et al. Kaposi's sarcoma in HIV-negative homosexual men. Lancet. 1990;335:168-9.
5. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266:1865-9.
6. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med. 1995;332:1186-91.
7. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood. 1995;86:1276-80.
8. Marmor M, Friedman-Kien AE, Laubenstein L, Byrum RD, William DC, D'onofrio S, et al. Risk factors for Kaposi's sarcoma in homosexual men. Lancet. 1982;1:1083-7.
9. Bayne D, Wise GJ. Kaposi sarcoma of penis and genitalia: a disease of our times. Urology. 1988;31:22-5.
10. Lowe FC, Lattimer DG, Metroka CE. Kaposi's sarcoma of the penis in patients with acquired immunodeficiency syndrome. J Urol. 1989;142:1475-7.
11. Grulich AE, Vajdic CM. The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. Semin Oncol. 2015;42:247-57.
12. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet. 1990;335:123-8.
13. International Agency for Reseach on Cancer. in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 100B (International Agency for Reseach on Cancer, 2012).
14. Roshan R, Labo N, Trivett M, Miley W, Marshall V, Coren L, et al. T-cell responses to KSHV infection: a systematic approach. Oncotarget. 2017;8:109402-16.
15. Bechtel JT, Liang Y, Hvidding J, Ganem D. Host range of Kaposi's sarcoma-associated herpesvirus in cultured cells. J Virol. 2003;77:6474-81.
16. Sarid R, Flore O, Bohenzky RA, Chang Y, Moore PS. Transcription mapping of the Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) genome in a body cavity-based lymphoma cell line (BC-1). J Virol. 1998;72:1005-12.

17. Cai X, Lu S, Zhang Z, Gonzalez CM, Damania B, Cullen BR. Kaposi's sarcoma-associated herpesvirus expresses an array of viral microRNAs in latently infected cells. Proc Natl Acad Sci U S A. 2005;102:5570-5.
18. Arvanitakis L, Geras-Raaka E, Varma A, Gershengorn MC, Cesarman E. Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. Nature. 1997;385:347-50.
19. Cavallin LE, Ma Q, Naipauer J, Gupta S, Kurian M, Locatelli P, et al. KSHV-induced ligand mediated activation of PDGF receptor-alpha drives Kaposi's sarcomagenesis. PLoS Pathog. 2018;14:e1007175.
20. Bower M, Dalla Pria A, Coyle C, Andrews E, Tittle V, Dhoot S, et al. Prospective stage-stratified approach to AIDS-related Kaposi's sarcoma. J Clin Oncol. 2014;32:409-14.
21. Kuriyama Y, Shimizu A, Yamada K, Yasuda M, Amano H, Tamura A, et al. Case of classic Kaposi sarcoma of the penis successfully treated with radiotherapy. J Dermatol. 2018;45:e175-e176.
22. De Rose AF, Justich M, Mantica G, Testino N, Terrone C. Kaposi's sarcoma: An unusual penile lesion in a HIV negative patient. Arch Ital Urol Androl. 2017;89:164-5.
23. Fairley JL, Denham I, Yoganathan S, Read TR. Topical imiquimod 5% as a treatment for localized genital Kaposi's sarcoma in an HIV-negative man: a case report. Int J STD AIDS. 2012;23:907-8.
24. Kampantais S, Gourvas V, Ioannidis S. Penile Kaposi's sarcoma in a HIV negative HHV-8 positive man. Hippokratia. 2013;17:96.
25. Lebari D, Gohil J, Patnaik L, Wasef W. Isolated penile Kaposi's sarcoma in a HIV-positive patient stable on treatment for three years. Int J STD AIDS. 2014;25:607-10.
26. Cecchi R, Troiano M, Ghilardi M, Bartoli L. Kaposi sarcoma of the penis in an HIV-negative patient. J Cutan Med Surg. 2011;15:118-20.
27. Karami H, Bagher-Tabrizi A, Yaghoobi M. Primary Kaposi Sarcoma of Penis in HIV Negative Patient. Iran J Cancer Prev. 2012 Fall;5:225-7.
28. Angulo JC, Lopez JI, Unda-Urzaiz M, Larrinaga JR, Zubiaur CL, Flores NC. Kaposi's sarcoma of the penis as an initial urological manifestation of AIDS. A report of two cases. Urol Int. 1991;46:235-7.
29. Gönen M, Cenker A, Kiyici H, Kalkan M. Penile Kaposi's sarcomas in a circumcised and HIV-seronegative patient. Int J Urol. 2006;13:318-20.
30. Kim KH, Choi JI, Ryu KH, Kang IH, Leng YH, Lee JW, et al. Primary Classic Kaposi's Sarcoma of the Penis in an HIV-Negative Patient. Korean J Urol. 2010;51:803-6.
31. Seleit I, Attia A, Maraee A, Samaka R, Bakry O, Eid E. Isolated Kaposi Sarcoma in two HIV negative patients. J Dermatol Case Rep. 2011;5:24-6.
32. Zargari O. Exclusive penile Kaposi's sarcoma: report of an HIV-negative man successfully treated with radiotherapy. J Eur Acad Dermatol Venereol. 2006;20:318-20.
33. Guevara JFA, Fernández SL, Claros OR, Villalta PG, Lostal JLC, Abarzuza MAR. Kaposi sarcoma of th e penis in anHIV-negative patient. Einstein (Sao Paulo). 2019;17:eRC4504.
34. Conger K, Sporer A. Kaposi sarcoma limited to glans penis. Urology. 1985;26:173-5.
35. Maiche AG, Holsti P, Gröhn P, Wasenius VM. Kaposi's sarcoma of penis. Br J Urol. 1986;58:557.
36. Marquart KH, Oehlschlaegel G, Engst R. Disseminated Kaposi's sarcoma that is not associated with acquired immunodeficiency syndrome in a bisexual man. Arch Pathol Lab Med. 1986;110:346-7.
37. Jaimovich L, Calb I, Kaminsky A. Kaposi's sarcoma of the conjunctiva. J Am Acad Dermatol. 1986;14:589-92.
38. Casado M, Jimenez F, Borbujo J, Almagro M. Spontaneous healing of Kaposi's angiosarcoma of the penis. J Urol. 1988;139:1313-5.
39. Zambolin T, Simeone C, Baronchelli C, Cunico SC. Kaposi's sarcoma of the penis. Br J Urol. 1989;63:645-6.
40. Lands RH, Ange D, Hartman DL. Radiation therapy for classic Kaposi's sarcoma presenting only on the glans penis. J Urol. 1992;147:468-70.
41. Myslovaty B, Kyzer S, Koren R, Chaimoff C. Kaposi sarcoma limited to the glans penis. Plast Reconstr Surg. 1993;92:764.
42. Guy M, Singer D, Barzilai N, Eisenkraft S. Primary classic Kaposi's sarcoma of glans penis--appearance on magnetic resonance imaging. Br J Urol. 1994;74:521-2.
43. Grunwald MH, Amichai B, Halevy S. Purplish penile papule as a presenting sign of Kaposi's sarcoma. Br J Urol. 1994;74:517.
44. Ruszczak Z, Stadler R, Schwartz RA. Kaposi's sarcoma limited to penis treated with cobalt-60 radiotherapy. J Med. 1996;27:211-20.
45. Koyuncuoğlu M, Yalçin N, Ozkan S, Kirkali Z. Primary Kaposi's sarcoma of the glans penis. Br J Urol. 1996;77:614-5.
46. Berkmen F, Celebioğlu AS. Adult genitourinary sarcomas: a report of seventeen cases and review of the literature. J Exp Clin Cancer Res. 1997;16:45-8.
47. Chun YS, Chang SN, Park WH. A case of classical Kaposi's sarcoma of the penis showing a good response to high-energy pulsed carbon dioxide laser therapy. J Dermatol. 1999;26:240-3.

48. Schwartz RA, Cohen JB, Watson RA, Gascón P, Ahkami RN, Ruszczak Z, et al. Penile Kaposi's sarcoma preceded by chronic penile lymphoedema. Br J Dermatol. 2000;142:153-6.

49. Kavak A, Akman RY, Alper M, Büyükbabani N. Penile Kaposi's sarcoma in a human immunodeficiency virus-seronegative patient. Br J Dermatol. 2001;144:207-8.

Gianmartin Cito, MD

Department of Urology
Careggi Hospital, University of Florence
Largo Brambilla, 3, 50134 Florence, Italy
Telephone: + 39 055 794-9203
E-mail: gianmartin.cito@gmail.com

ARTICLE INFO

Gianmartin Cito
http://orcid.org/0000-0001-7526-4025

Int Braz J Urol. 2020; 46: 825-42

Submitted for publication:
July 02, 2019

Accepted after revision:
October 06, 2019

Published as Ahead of Print:
November 30, 2019

UPDATE IN UROLOGY

NEURO-UROLOGY

Vol. 46 (5): 843-844, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.04

Editorial Comment: An Effective Evidence-Based Cleaning Method for the Safe Reuse of Intermittent Urinary Catheters: In Vitro Testing

Wilks SA [1, 2], Morris NS [3], Thompson R [3], Prieto JA [1], Macaulay M [1], Moore KN [4], et al.

[1] School of Health Sciences, Faculty of Environmental and Life Sciences, University of Southampton, Highfield Southampton, UK; [2] School of Biological Sciences, Faculty of Environmental and Life Sciences, University of Southampton, Highfield Southampton, UK; [3] Bristol Urological Institute, North Bristol NHS Trust, Southmead Hospital, Bristol, UK; [4] Faculty of Nursing, University of Alberta, Edmonton, Canada

Neurourol Urodyn. 2020 Mar;39(3):907-915

DOI: 10.1002/nau.24296 | ACCESS: 10.1002/nau.24296

Marcio Augusto Averbeck [1], Blayne Welk [2]

[1] Chefe de Neuro-Urologia, Unidade de Videourodinâmica, Hospital Moinhos de Vento. Porto Alegre, RS, Brasil; [2] Department of Surgery and Epidemiology & Biostatistics, Western University, London ON Canada

COMMENT

The article published by Wilks et al. (1) is a nice contemporary examination of the in vitro performance of different types of cleaning methods for uncoated urinary catheters. Their methods advance the work of previous studies as they used two types of artificial urine media, assessed for viable but nonculturable bacteria (bacteria which are just "stunned" but could still potentially cause an infection), and assessed surface structural damage. While many of the traditional methods did well and were able to eliminate culturable bacteria, these methods often resulted in the development of "stunned" bacteria. The 3 heat-based methods (steam, boiling, microwave) all changed the mechanical properties of the catheters. Ultrasonic cleaning and vinegar showed evidence of viable but nonculturable bacteria populations, indicating the methods were bacteriostatic. Detergent and water wash followed by immersion in a commercially available 0.6% sodium hypochlorite solution and 16.5% sodium chloride (diluted Milton) gave consistent bactericidal results and no visible catheter damage.

While there is good agreement that intermittent catheterization (IC) represents the ideal method of managing a bladder that fails to empty, the optimal way to do IC is still a subject of controversy. The options around single use/multiple use, and the relative benefit of different types of catheter coatings are still debated. A recent, well done randomised trial in patients with spina bifida did not show a benefit in terms of UTI

reduction over 8 weeks when intermittent catheters were reused compared to when catheters were only used once (35.2% vs 36.8%, p=0.877) (2). It is still common for patients to reuse uncoated catheters for IC (for example in Brazil, Canada and many developing countries), and thus the question about caring for reused catheters is still relevant.

Hydrophilic catheters have been introduced to the urological practice as an alternative to reduce the risk of recurrent UTI and urethral trauma (3). However, associated costs are higher in comparison to clean intermittent catheterization (CIC), which has been the standard since it was proposed by Lapides decades ago (4). One of the most frustrating things for patients is the lack of information from physicians about how to practically reuse catheters. In the neurogenic population, complex methods add an additional burden to a person's daily routine. Over the years, patients have described varied routines, ranging from using one catheter a week and rinsing it in tap water, to more complex cleaning processes involving vinegar, dilute bleach, freezing and microwaving.

Despite the promising laboratory results published by Wilks et al, clinical studies are still needed to check whether diluted Milton strategy is effective and safe for patients. Bacterial biofilm still represents an important barrier for patients who reuse catheters (5). A general limitation of most uncoated PVC catheters is that they contain softeners such as phthalates that may put the users at risk of certain diseases (6). In the general population, exposure to some phthalate diesters is a cause of increasing concern because of their potential adverse effects on the reproductive and endocrine systems (7).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wilks SA, Morris NS, Thompson R, Prieto JA, Macaulay M, Moore KN, et al. An effective evidence-based cleaning method for the safe reuse of intermittent urinary catheters: In vitro testing. Neurourol Urodyn. 2020;39:907-15.
2. Madero-Morales PA, Robles-Torres JI, Vizcarra-Mata G, Guillén-Lozoya AH, Mendoza-Olazarán S, Garza-González E, et al. Randomized Clinical Trial Using Sterile Single Use and Reused Polyvinylchloride Catheters for Intermittent Catheterization with a Clean Technique in Spina Bifida Cases: Short-Term Urinary Tract Infection Outcomes. J Urol. 2019;202:153-8.
3. Li L, Ye W, Ruan H, Yang B, Zhang S, Li L. Impact of hydrophilic catheters on urinary tract infections in people with spinal cord injury: systematic review and meta-analysis of randomized controlled trials. Arch Phys Med Rehabil. 2013;94:782-7.
4. Lapides J, Diokno AC, Silber SJ, Lowe BS. Clean, intermittent self-catheterization in the treatment of urinary tract disease. J Urol. 1972;107:458-61.
5. Biering-Sørensen F. Urinary tract infection in individuals with spinal cord lesion. Curr Opin Urol. 2002;12:45-9.
6. Truzzi JC, Teich V, Pepe C. Can hydrophilic coated catheters be beneficial for the public healthcare system in Brazil? - A cost-effectiveness analysis in patients with spinal cord injuries. Int Braz J Urol. 2018;44:121-31.
7. Cutanda F, Koch HM, Esteban M, Sánchez J, Angerer J, Castaño A. Urinary levels of eight phthalate metabolites and bisphenol A in mother-child pairs from two Spanish locations. Int J Hyg Environ Health. 2015;218:47-57.

Marcio Averbeck, MD, PhD

Unidade de Videourodinâmica, Hospital Moinhos de Vento. Porto Alegre, RS, Brasil
E-mail: marcio@averbeck.com.br

ARTICLE INFO

Marcio Averbeck
https://orcid.org/0000-0002-8127-7153

Int Braz J Urol. 2020; 46: 843-4

UPDATE IN UROLOGY

ENDOUROLOGY

Vol. 46 (5): 845-846, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.05

Editorial Comment: Techniques - Ultrasound-guided percutaneous nephrolithotomy: How we do it

Beiko D [1], Razvi H [2], Bhojani N [3], Bjazevic J [2], Bayne DB [4], Tzou DT [5], et al.

[1] Department of Urology, Queen's University, Kingston, ON, Canada; [2] Division of Urology, Department of Surgery, Western University, London, ON, Canada; [3] Division of Urology, Université de Montréal, Montreal, QC, Canada; [4] Department of Urology, University of California at San Francisco, San Francisco, CA, United States; [5] Division of Urology, Department of Surgery, University of Arizona College of Medicine, Tucson, AZ, United States

Can Urol Assoc J. 2019 Sep 27. [Epub ahead of print]

DOI: 10.5489/cuaj.6076 | ACCESS: 10.5489/cuaj.6076

Alexandre Danilovic [1]

[1] Serviço de Urologia, Hospital das Clínicas da Faculdade de Medicina da USP - HCFMUSP, São Paulo, SP, Brasil

COMMENT

Ultrasound-guided percutaneous nephrolithotomy (US-PNL) has gained popularity in many parts of the world in the past few years (1). It may be used in combination with fluoroscopy to reduce ionizing radiation exposure or replacing fluoroscopy to completely eliminate exposure to radiation during PNL (2). However, this technique can be challenging to learn.

This article provides some interesting key points for those who would like to start a US-PNL program. Despite other authors claim no different results for obese vs. non-obese patients (3), according to the authors, the ideal candidate to start a learning curve of US-PNL is a healthy non-obese patient whose imaging demonstrates a non-staghorn calculus and at least moderate hydronephrosis. The authors described in details eight steps for a successful US-PNL.

There are many advantages of the use of ultrasound in PNL and this technique should be encouraged. However, some anatomic details of the collecting system are missed by ultrasound. Therefore, it is recommended to progressively convert fluoroscopy to ultrasound guidance step-by-step as one gains experience. More important than completely eliminate exposure to radiation is to keep patient safe from injuries due to suboptimal image guidance.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. TLi J, Xiao B, Hu W, Yang B, Chen L, Hu H, et al. Complication and safety of ultrasound guided percutaneous nephrolithotomy in 8,025 cases in China. Chin Med J (Engl). 2014;127:4184-9.
2. Zhu W, Li J, Yuan J, Liu Y, Wan SP, Liu G, et al. A prospective and randomised trial comparing fluoroscopic, total ultrasonographic, and combined guidance for renal access in mini-percutaneous nephrolithotomy. BJU Int. 2017;119:612-8.
3. Jin W, Song Y, Fei X. Does Body Mass Index Impact the Outcomes of Ultrasound-Guided Percutaneous Nephrolithotomy? Urol Int. 2019;103:149-55.

Alexandre Danilovic, MD

Serviço de Urologia, Hospital das Clínicas da Faculdade de Medicina da USP - HCFMUSP, São Paulo, SP, Brasil
E-mail: alexandre.danilovic@gmail.com

ARTICLE INFO

Alexandre Danilovic
https://orcid.org/0000-0002-6963-6117

Int Braz J Urol. 2020; 46: 845-6

UPDATE IN UROLOGY

ENDOUROLOGY

Vol. 46 (5): 847-848, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.06

Editorial Comment: The significance of intraoperative renal pelvic urine and stone cultures for patients at a high risk of post-ureteroscopy systemic inflammatory response syndrome

Yoshida S [1], Takazawa R [2], Uchida Y [1], Kohno Y [1], Waseda Y [1], Tsujii T [1]

[1] Department of Urology, Kidney Stone Center, Tokyo Metropolitan Ohtsuka Hospital, 2-8-1 Minami-Ohtsuka, Toshima-ku, Tokyo, 170-8476, Japan; [2] Department of Urology, Kidney Stone Center, Tokyo Metropolitan Ohtsuka Hospital, 2-8-1 Minami-Ohtsuka, Toshima-ku, Tokyo, 170-8476, Japan

Urolithiasis. 2019 Dec;47(6):533-540

DOI: 10.1007/s00240-019-01112-6 | ACCESS: 10.1007/s00240-019-01112-6

Alexandre Danilovic [1]

[1] Serviço de Urologia, Hospital das Clínicas da Faculdade de Medicina da USP - HCFMUSP, São Paulo, SP, Brasil

COMMENT

Infectious complications are among the most feared complications of retrograde intrarenal surgery (RIRS). Untreated positive pre-operative bladder urine culture (PBUC) is a contraindication for RIRS, but infectious complications may occur even with prophylactic antibiotics and negative PBUC (1). The role of renal pelvic urine culture (RPUC) and stone culture (SC) are well known in patients undergoing percutaneous nephrolithotomy (2). However, its role in RIRS is not established.

This prospective study investigated the associations among the results of PBUC, RPUC, and SC. PBUC was positive in 49.6% of the patients. Even after adequate antibiotic administration, RPUC was positive in 19.2% and SC was positive in 15.2% of the patients. Moreover, bacterial species detected by PBUC were not necessarily consistent with those of RPUC and/or SC. Systemic inflammatory response syndrome (SIRS) occurred in 10.3% of the patients. Female gender (OR=2.81), struvite calculi (OR=4.95) and positive RPUC (OR=3.83) were significant risk factors of SIRS after RIRS.

Therefore, obtaining a RPUC during RIRS is highly recommended because it can be useful for selecting appropriate antibiotics.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69:475-82.
2. Mariappan P, Smith G, Bariol SV, Moussa SA, Tolley DA. Stone and pelvic urine culture and sensitivity are better than bladder urine as predictors of urosepsis following percutaneous nephrolithotomy: a prospective clinical study. J Urol. 2005;173:1610-4.

Alexandre Danilovic, MD

Serviço de Urologia, Hospital das Clínicas da Faculdade de Medicina da USP - HCFMUSP, São Paulo, SP, Brasil
E-mail: alexandre.danilovic@gmail.com

ARTICLE INFO

Alexandre Danilovic
https://orcid.org/0000-0002-6963-6117

Int Braz J Urol. 2020; 46: 847-8

UPDATE IN UROLOGY

ENDOUROLOGY

Vol. 46 (5): 849-850, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.07

Editorial Comment: Safety of a Novel Thulium Fiber Laser for Lithotripsy: An In Vitro Study on the Thermal Effect and Its Impact Factor

Peng Y [1], Liu M 1, Ming S [1], Yu W [2], Li L [1], Lu C [1], et al.

[1] Department of Urology, Shanghai Changhai Hospital, Shanghai, China; [2] Department of Urology, Shaoxing Shangyu People's Hospital, Zhejiang, China

J Endourol. 2020 Jan;34(1):88-92

DOI: 10.1089/end.2019.0426 | ACCESS: 10.1089/end.2019.0426

Alexandre Danilovic [1]

[1] Serviço de Urologia, Hospital das Clínicas da Faculdade de Medicina da USP - HCFMUSP, São Paulo, SP, Brasil

COMMENT

Thulium fiber laser (TFL) is composed of silica fiber doped with Thulium ions triggered during the laser activation. Since 2005, TFL has been evaluated in several preclinical studies for the management of urolithiasis (1). Previous in vitro studies showed TFL produced faster stone ablation rates, smaller stone fragments and lower retropulsion than the Holmium:YAG laser (2, 3). However, the specific heat production of TFL is four times higher than that of the Holmium:YAG laser (2). Irrigation rate and laser power settings are critical to avoid biological damage due to thermal effect of Holmium:YAG laser (4). Therefore, it is important to know the major determinants of thermal effect of TFL.

This in vitro study evaluated the impact of different TFL power settings and irrigation rates on water temperature. The investigators used a novel TFL prototype (Raykeen Laser Technology Limited Corporation, Shanghai, China) with a maximum power output of 55W in super pulse mode with 272 µm core diameter fiber. The safety threshold of temperature for laser surgery was established in 43° C. This study found TFL power ≥ 15W may cause heat injury of tissues when irrigation is ceased during lithotripsy. TFL power up to 30 W was safe with a moderate irrigation rate of 15 mL/min. The authors recommend irrigation rate ≥ 25 mL/min or intermittent laser firing when using TFL power above 30W.

Although this study established in vitro safety irrigation rates and power settings for the thermal effect of TFL, the authors did not tested different fiber sizes. Fiber size influences irrigation rates. Therefore, future studies are needed to elucidate the thermal effect of TFL using smaller fibers and its influence using animal models.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Fried NM. Thulium fiber laser lithotripsy: an in vitro analysis of stone fragmentation using a modulated 110-watt Thulium fiber laser at 1.94 microm. Lasers Surg Med. 2005;37:53-8.
2. Andreeva V, Vinarov A, Yaroslavsky I, Kovalenko A, Vybornov A, Rapoport L, et al. Preclinical comparison of superpulse thulium fiber laser and a holmium:YAG laser for lithotripsy. World J Urol. 2020;38:497-503.
3. Hardy LA, Vinnichenko V, Fried NM. High power holmium:YAG versus thulium fiber laser treatment of kidney stones in dusting mode: ablation rate and fragment size studies. Lasers Surg Med. 2019;51:522-30.
4. Hein S, Petzold R, Schoenthaler M, Wetterauer U, Miernik A. Thermal effects of Ho: YAG laser lithotripsy: real-time evaluation in an in vitro model. World J Urol. 2018;36:1469-75.

Alexandre Danilovic, MD

Serviço de Urologia, Hospital das Clínicas da Faculdade de Medicina da USP - HCFMUSP, São Paulo, SP, Brasil
E-mail: alexandre.danilovic@gmail.com

ARTICLE INFO

Alexandre Danilovic
https://orcid.org/0000-0002-6963-6117

Int Braz J Urol. 2020; 46: 849-50

UPDATE IN UROLOGY

MALE HEALTH

Vol. 46 (5): 851-852, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.08

Editorial Comment: The Basic Physics of Waves, Soundwaves, and Shockwaves for Erectile Dysfunction

Katz JE [1], Clavijo RI [2], Rizk P [1], Ramasamy R [3]

[1] Department of Urology, University of Miami, Miami, FL, USA; [2] Department of Urology, University of California at Davis, Davis, CA, USA; [3] Department of Urology, University of Miami, Miami, FL, USA

Sex Med Rev. 2020 Jan;8(1):100-105

DOI: 10.1016/j.sxmr.2019.09.004 | ACCESS: 10.1016/j.sxmr.2019.09.004

Valter Javaroni [1]

[1] Departamento de Andrologia, Hospital Federal do Andaraí Rio de Janeiro, Rio de Janeiro, RJ, Brasil

COMMENT

Dr. Jonathan Elliott Katz and cols., taking into consideration that Li-ESWT is not U.S. Food and Drug Administration approved and is considered investigational in the United States and available to patients under clinical trial protocols, made a nice review on the physic aspects of shockwaves. And drive attention to the aspect that each device should use the protocol approved for it.

In 2010, Vardi et al. (1) published their first paper, which introduced the use of low intensity extracorporeal shock wave therapy (LI-ESWT) for ED. Since them, many articles have been published communicating safety and efficacy of Li-ESWT in ED patients (2). The results of studies with a small number of patients and a short observation period were encouraging, but we live with the diversity of devices and the lack of clear protocols, mainly in special populations.

In a recent report, Dr. Fojecki and cols. (3) presented 6- and 12-month data from a randomized, sham-controlled trial on LI-ESWT for ED and did not find any clinically significant effect between two different protocols.

According to another recent publication on Journal of Sexual Medicine (4): "*These studies provide preliminary insights, but no definitive answers, and many questions remain unanswered regarding the mechanism of action, as well as the ideal treatment protocol*".

However, there is a need to define which subgroup of ED population is best suited and the most appropriated LI-ESWT treatment protocol including template, modality of shockwaves energy, emission frequency, and total energy delivery.

So, we still do require better design studies with clear inclusion and exclusion criteria using validated tools to access erectile function improvement in long follow up periods. Ideally we should do it before treating our patients.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. AVardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol. 2010;58:243-8.
2. Clavijo RI, Kohn TP, Kohn JR, Ramasamy R. Effects of Low-Intensity Extracorporeal Shockwave Therapy on Erectile Dysfunction: A Systematic Review and Meta-Analysis. J Sex Med. 2017;14:27-35.
3. Fojecki GL, Tiessen S, Osther PJS. Effect of Linear Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction-12-Month Follow-Up of a Randomized, Double-Blinded, Sham-Controlled Study. Sex Med. 2018;6:1-7.
4. Sokolakis I, Dimitriadis F, Teo P, Hatzichristodoulou G, Hatzichristou D, Giuliano F. The Basic Science Behind Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction: A Systematic Scoping Review of Pre-Clinical Studies. J Sex Med. 2019;16:168-94.

Valter Javaroni, MD

Departamento de Andrologia,
Hospital Federal do Andaraí Rio de Janeiro,
Rio de Janeiro, RJ, Brasil
E-mail: drjavaroni2000@yahoo.com.br

ARTICLE INFO

Valter Javaroni
https://orcid.org/0000-0003-3877-0601

Int Braz J Urol. 2020; 46: 851-2

UPDATE IN UROLOGY

PROSTATE CANCER

Vol. 46 (5): 853-854, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.09

Editorial Comment: Cardiovascular Morbidity in a Randomized Trial Comparing GnRH Agonist and GnRH Antagonist among Patients with Advanced Prostate Cancer and Preexisting Cardiovascular Disease

Margel D [1,2], Peer A [3], Ber Y [1], Shavit-Grievink L [1,4], Tabachnik T [1], Sela S [1], et al.

[1] Division of Urology, Rabin Medical Center, Petach Tikva, Israel; [2] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3] Department of Oncology, Rambam Health Care Campus and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [4] Davidoff Cancer Centre, Rabin Medical Center, Petach Tikva, Israel

J Urol. 2019 Dec;202(6):1199-1208.

DOI: 10.1097/JU.0000000000000384 | ACCESS: 10.1097/JU.0000000000000384

Felipe Lott [1]

[1] Instituto Nacional do Câncer – INCA, Rio de Janeiro, RJ, Brasil

COMMENT

Retrospective studies have shown an association between androgen deprivation therapy (ADT) and an increase risk of cardiovascular disease (CVD) (1,2).

This paper is the first randomized study (phase II) on cardiovascular morbidity with high risk or metastatic prostate cancer patients with previous CVD events (CVDes) (37% experienced a myocardial infarction within a year before randomization) and treated with GnRh agonist (with 2 times more diabetes patients) or GnRh antagonist by one year period time.

The primary endpoint was to compare endothelial function using the EndoPAT 2000 device (3) that appears to predict cardiovascular outcomes (4). The secondary endpoint was CVDes.

There was no difference in the primary endpoint between the 2 groups but it occurred in the secondary one (more subject to statistical error) with 3% of major cardiovascular and cerebrovascular event in the GnRh antagonist group and 20% in the GnRh agonist one (p=0.013).

Maybe it is not appropriate to compare arms of a phase II trial especially in this small one. A large phase III trial (PRONOUNCE study) may define it better but, until now, an alert has been sent in patients with preexisting CVD (especially with a new event in the last 12 months).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Hu JC, Williams SB, O'Malley AJ, Smith MR, Nguyen PL, Keating NL. Androgen-deprivation therapy for nonmetastatic prostate cancer is associated with an increased risk of peripheral arterial disease and venous thromboembolism. Eur Urol. 2012;61:1119-28.
2. Jespersen CG, Nørgaard M, Borre M. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. Eur Urol. 2014;65:704-9.
3. McCrea CE, Skulas-Ray AC, Chow M, West SG. Test-retest reliability of pulse amplitude tonometry measures of vascular endothelial function: implications for clinical trial design. Vasc Med. 2012;17:29-36.
4. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J. 2010;31:1142-8.

Felipe Lott, MD

Instituto Nacional do Câncer – INCA
Rio de Janeiro, RJ, Brasil
E-mail: felipelott@hotmail.com

ARTICLE INFO

Felipe Lott
https://orcid.org/0000-0001-5678-5343

Int Braz J Urol. 2020; 46: 853-4

UPDATE IN UROLOGY

PROSTATE CANCER

Vol. 46 (5): 855-856, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.05.10

Editorial Comment: Randomised Trial of Adjuvant Radiotherapy Following Radical Prostatectomy Versus Radical Prostatectomy Alone in Prostate Cancer Patients with Positive Margins or Extracapsular Extension

Hackman G [1], Taari K [2], Tammela TL [3], Matikainen M [2], Kouri M [4], Joensuu T [5], et al.

[1] Faculty of Medicine, University of Helsinki, Helsinki, Finland; [2] Department of Urology, Helsinki University Hospital, Helsinki, Finland; [3] Department of Surgery, Tampere University Hospital, Faculty of Medicine and Life Sciences, Tampere University, Tampere, Finland; [4] Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; [5] Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; Docrates Cancer Center, Helsinki, Finland

Eur Urol. 2019 Nov;76(5):586-595

DOI: 10.1016/j.eururo.2019.07.001 | ACCESS: 10.1016/j.eururo.2019.07.001

Felipe Lott [1]

[1] Instituto Nacional do Câncer – INCA, Rio de Janeiro, RJ, Brasil

COMMENT

The latest guideline suggest adjuvant radiotherapy or observation following prostatectomy with adverse pathological findings (1, 2). This trial randomized 250 patients (1:1) with pT2N0M0 with positive margins or pT3aN0M0 and tries to answer if there is a benefit from adjuvant radiotherapy after radical prostatectomy. The postoperative PSA was less than 0.5. The median follow-up for alive patients was 9.3 yr and 8.6 yr in the adjuvant and in the observation group respectively. The primary endpoint was biochemical recurrence-free survival (BCRFs) and the overall survival, cancer-specific survival, and adverse events were the secondary ones.

The authors founded a 74% benefit of BCRFs in the adjuvant group, and the number needed to treat was 4. There were no difference in the overall survival and in cancer-specific survival, with more grade 1 and 2 adverse events in the adjuvant group.

The first results of the RADICALS trial (NCT 005541047) recently presented at ESMO Congress 2019 did not show any benefit in BCRFs (secondary endpoint), supporting the use of early salvage radiotherapy.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17:479-505.
2. Mottet N, Cornford P, van den Bergh RCN, Briers E, De Santis M, Fanti S, et al. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. available at. <https://uroweb.org/guideline/prostate-cancer> accessed July 11, 2019.

Felipe Lott, MD

Instituto Nacional do Câncer – INCA
Rio de Janeiro, RJ, Brasil
E-mail: felipelott@hotmail.com

ARTICLE INFO

Felipe Lott
https://orcid.org/0000-0001-5678-5343

Int Braz J Urol. 2020; 46: 855-6

RADIOLOGY PAGE

Vol. 46 (5): 857-858, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0415

Ureteroinguinal hernia with obstructive urolithiasis

JuliAnne R. Rathbun [1, 2], Nanda Thimmappa [3], Stephen H. Weinstein [1, 2], Katie S. Murray [1, 2]

[1] Division of Urology, University of Missouri School of Medicine, Columbia, Missouri, USA; [2] Department of Surgery University of Missouri School of Medicine, Columbia, Missouri, USA; [3] Department of Radiology, University of Missouri School of Medicine, Columbia, Missouri, USA

CASE REPORT

A 64-year-old male was referred for elevated PSA of 13.7ng/mL. He underwent transrectal ultrasound-guided prostate biopsy and was found to have Gleason 4+4 prostate cancer. Staging computed tomography (CT) revealed mild left renal atrophy and left hydroureteronephrosis. The dilated ureter extended down through the left inguinal canal and into the left hemiscrotum, where a 1cm stone was noted within a ureteroinguinal hernia (Figure I). The right ureter was also contained within a right ureteroinguinal hernia, but was not dilated. Bone scan showed retained contrast in the left distal ureter within the hernia (Figure II). The patient endorsed mild back pain that he attributed to lifting and physical activity. He had a history of hypertension, and his creatinine had elevated to 1.7mg/dL over the last two years. He was evaluated by general surgery, and his bilateral inguinal hernias were noted to be non-palpable.

Inguinal hernias can be direct or indirect and have the lifetime risk of development of 27-43% in men and 3-6% in women (1-3). Risk factors for inguinal hernia development include increased age, low body mass index (BMI) and genetic mutations altering connective tissue (1). Indirect hernia risk factors are patent processus vaginalis and increased cumulative occupational mechanical exposure (1). A unique subdivision of indirect inguinal hernias is ureteroinguinal. Of the two types of ureteroinguinal hernias, the most common are paraperitoneal (80%), which are associated with a peritoneal evagination (4, 5). Extraperitoneal ureteroinguinal hernias involve the ureter alone or with retroperitoneal fat (4-6). In the literature, around 140 cases have been described, and very few of these with obstructive uropathy (6, 7). Management involves herniorrhaphy with a team-based approach between general surgery and urology (8). Risk of recurrence after standard repair increases with elevated intraabdominal pressures, which can be secondary to high BMI (1).

The patient underwent bilateral laparoscopic inguinal hernia repair with subsequent left ureteroscopy for his stone. His ureter was noted to be extremely elongated and tortuous after hernia repair. His creatinine peaked at 2.3mg/dL at time of hernia repair, and then it improved to 1.6mg/dL by the time of ureteroscopy. He has recovered well from both surgeries and is planning to undergo fluciclovine F-18 scan for further staging of his prostate cancer. His hydroureteronephrosis was persistent on his immediately post-operative CT scan.

CONFLICT OF INTEREST

None declared.

Figure 1 - Coronal contrast-enhanced CT in nephrographic phase demonstrating left hydroureteronephrosis (*). Dilated left ureter noted to pass through inguinal canal (double arrows) and into the left hemiscrotum containing a stone (single arrow).

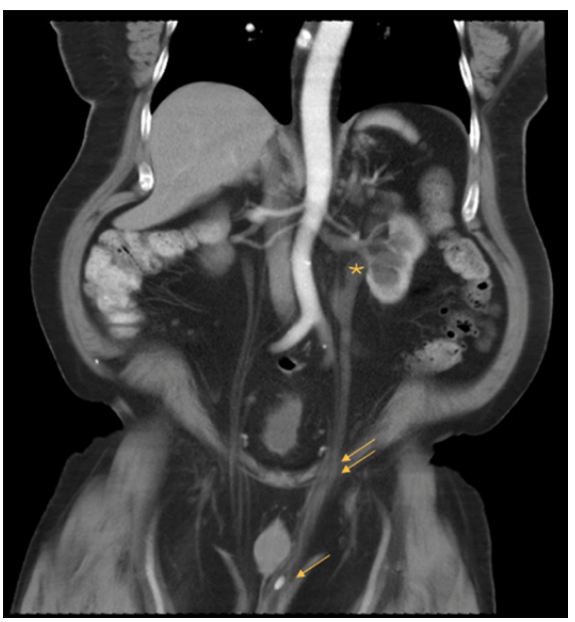
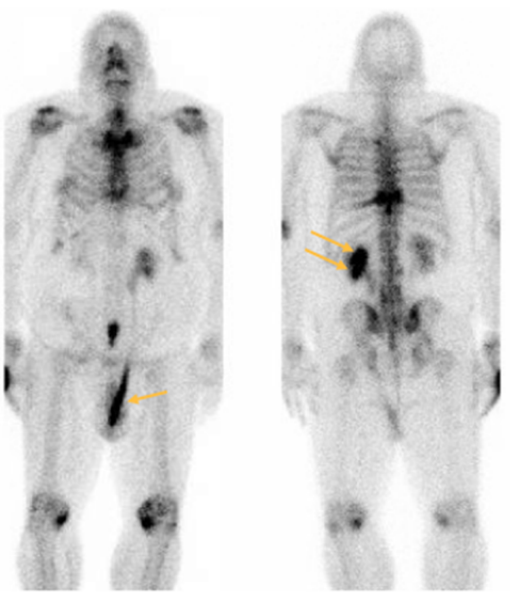


Figure 2 - Coronal bone scan showing retained contrast within left scrotal ureter (arrow) on the anterior view and slow drainage from the left kidney (double arrow) on the posterior view.



REFERENCES

1. Öberg S, Andresen K, Rosenberg J. Etiology of Inguinal Hernias: A Comprehensive Review. Front Surg. 2017;4:52.
2. Köckerling F, Simons MP. Current Concepts of Inguinal Hernia Repair. Visc Med. 2018;34:145-50.
3. HerniaSurge Group. International guidelines for groin hernia management. Hernia. 2018;22:1-165.
4. Zarraonandia Andraca A, Ríos Reboledo A, Casas Nebra J, Ponce Díaz-Reixa J, Martínez Breijo S, González Dacal J, et al. [Inguinal ureteral hernia: a clinical case]. Arch Esp Urol. 2009;62:755-7.
5. Roach SC, Moulding F, Hanbidge A. Inguinal herniation of the ureter. AJR Am J Roentgenol. 2005;185:283.
6. Yahya Z, Al-Habbal Y, Hassen S. Ureteral inguinal hernia: an uncommon trap for general surgeons. BMJ Case Rep. 2017;2017.
7. McKay JP, Organ M, Bagnell S, Gallant C, French C. Inguinoscrotal hernias involving urologic organs: A case series. Can Urol Assoc J. 2014;8:E429-32.
8. Eilber KS, Freedland SJ, Rajfer J. Obstructive uropathy secondary to ureteroinguinal herniation. Rev Urol. 2001;3:207-8.
9. E S A, D Y J, S G G, F E J. Inguinoscrotal herniation of the ureter: Description of five cases. Int J Surg Case Rep. 2015;14:160-3.
10. Ballard JL, Dobbs RM, Malone JM. Ureteroinguinal hernia: a rare companion of sliding inguinal hernias. Am Surg. 1991;57:720-2.

Correspondence address:
JuliAnne R. Rathbun, MD
Department of Surgery, Division of Urology,
University of Missouri
1 Hospital Drive, Columbia, MO 65212
E-mail: rathbunj@health.missouri.edu

ARTICLE INFO

JuliAnne R. Rathbun
http://orcid.org/0000-0002-5436-3224

Int Braz J Urol. 2020; 46: 857-8

Submitted for publication:
June 24, 2019

Accepted after revision:
November 06, 2019

Published as Ahead of Print:
April 20, 2020

RADIOLOGY PAGE

Vol. 46 (5): 859-863, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0180

Primary large cell prostate neuroendocrine carcinoma with central and nephrogenic diabetes insipidus

Cem Basatac [1], Sezer Sağlam [2], Fatma Aktepe [3], Haluk Akpinar [1]

[1] Department of Urology, Istanbul Bilim University, Istanbul, Turkey; [2] Department of Medical Oncology, Istanbul Bilim University, Istanbul, Turkey; [3] Department of Pathology, Group Florence Nightingale Hospitals, Istanbul, Turkey

INTRODUCTION

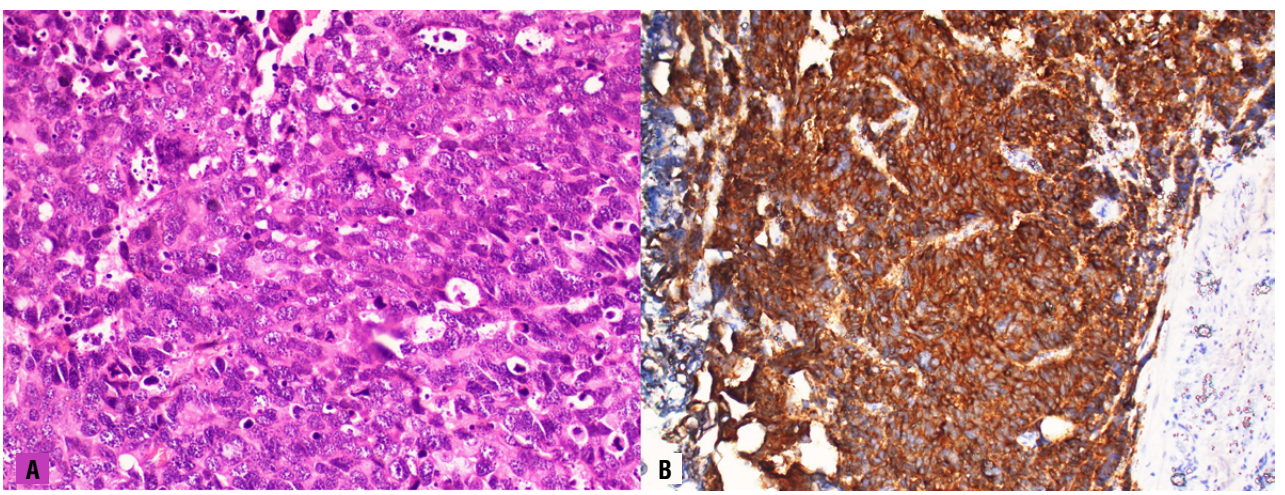
Neuroendocrine carcinoma of the prostate (PNEC) is rare and accounts for less than 0.5% of all prostate neoplasms (1). These tumors can be subdivided into small cell carcinomas, large cell neuroendocrine carcinomas (LCNEC) and carcinoid tumors based on the morphologic characteristics and proliferative index of tumors. PNEC is often diagnosed after long-lasting androgen deprivation therapy (ADT) for previous prostate adenocarcinoma (2). However, the pure form of this tumor is exceedingly rare and associated with aggressive behavior. Only a few cases with primary LCNEC have been published and its clinical course and treatment options remain unclear, yet (2, 3). In this study, we aim to report an unusual case of primary LCNEC with dexamethasone induced nephrogenic diabetes insipidus (NDI) during its management.

CASE DESCRIPTION

A seventy-year-old male patient was admitted to our hospital with complaints of dysuria, hematuria, and stranguria lasting for four weeks. He also suffered from chronic constipation. He had a previous prostate biopsy in 2005 and pathology was benign prostate hyperplasia. There was no prior history of surgical procedures and significant comorbidities in his past medical history. Physical examination revealed abdominal distention but without significant tenderness. A large-sized fixed prostate that was completely adhering to the pelvic wall was detected on digital rectal examination. The serum creatinine and prostate-specific antigen values were 9.96mg/dL and 3.9ng/dL, respectively. Ultrasonography showed bilateral grade two hydronephrosis and suspicious mass invading through the bladder neck and trigone. A Foley catheter was inserted to achieve urinary drainage. However, oliguria was not resolved with conservative treatments and serum creatinine showed a gradually increasing trend.

A cystoscopy revealed massive prostatic mass invading bladder neck and trigone. A channel transurethral resection of the prostate was carried out in order to visualize obstructed ureteral orifices. After then, Resonance® ureteral metal stents (Cook Urologic, Spencer, IN) were placed bilaterally under fluoroscopy guidance. A sextant transrectal prostate biopsy was also performed at the end of the procedure. Serum creatinine was normal at the postoperative 10th day. Pathologic examination revealed LCNEC on both specimens. In tumor cell nuclei, some of them had prominent nucleoli and most of them had salt and pepper appearance (Figure-1). Geo-

Figure 1A) The tumor cells were large with a high nuclear/cytoplasmic ratio, severe atypia, and prominent nucleoli or salt and pepper appearance. Numerous mitotic figures and apoptotic bodies were observed (H&E, × 400). B) Immunohistochemically, the tumor cells were positive for synaptophysin (x 400).



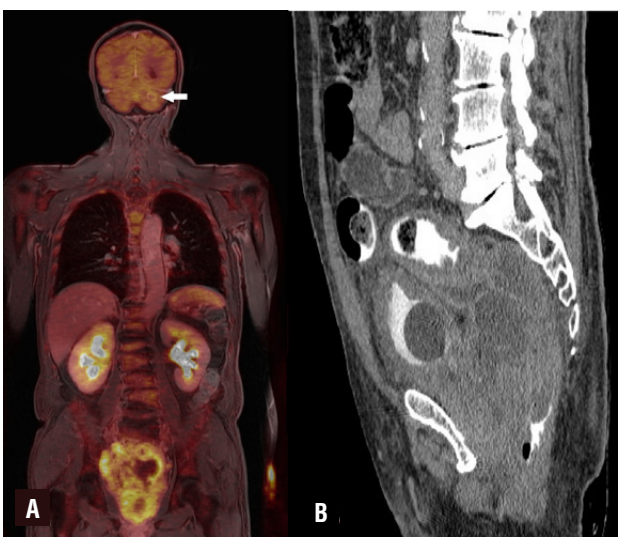
graphic tumor necroses were also noted. Immunohistochemistry was used to ensure pathologic diagnoses. Whereas immunohistochemical stains showed diffusely positive staining for synaptophysin, tumor cell was not stained with the common prostate adenocarcinoma markers such as PSA, AMACR, ERG, and GATA3, CK7, CK20. Additionally, tumor cell proliferation as assessed by the Ki-67 index was so high (95%). PET-MR showed an irregular mass measuring 15x12x9 cm that originates from the prostate with higher SUVmax [10] and invading to the rectosigmoid colon causing subtotal obstruction. 18^{F}- FDG uptake was positive in bilateral iliac and left paraaortic lymph nodes. A 6 cm metastatic lesion was noted on his posteromedial part of left femur diaphysis. In addition, PET-MR also showed brain metastases located at cerebellum and left parietal lobe (Figure-2).

We started classic systemic chemotherapy with cisplatin-etoposide. After the first session of the chemotherapy, his urine output increased significantly to 7000 cc/day with urine osmolality of 154 mOsm/kg suggesting central diabetes insipidus and it was normalized by desmopressin 120 mcg oral lyophilisate. Rectal stenosis due to mass effect of LCNEC was treated by a colorectal stent. Stereotactic body radiotherapy (SBRT) was performed to control the metastatic brain tumor growth using marginal doses of 20 Gy for metastatic lesions in the left parietal lobe and 24 Gy for the cerebellar lesion. However, 24 hours later there was an increased urine output again after a dexamethasone 8mg was started as a standard protocol at the same time of SBRT. It was unresponsive to treatment with desmopressin nasal spray, subcutaneous injection and regressed in 24 hours spontaneously when the dexamethasone was stopped after radiotherapy. Although primary tumor tended to shrink at the 3^{rd} months follow-up, a CT scan showed that primary, as well as the metastatic tumors, had progressed, and the patient died at the postoperative 7^{th} month due to multiple organ dysfunction.

DISCUSSION

Large cell neuroendocrine carcinoma of the prostate can be considered as one of the most lethal and aggressive subsets of prostate cancers (4). Aggressive behavior of this tumor is usually related to loss of androgen receptor signaling pathways which causes castration-resistant prostate cancer. Therefore, differential diagnoses are essential with a precise pathologic examination

Figure 2A) Coronal view of the tumor with PET-MR. (White arrow shows cerebellar metastases), B) Sagittal reconstruction of CT images showing tumor compression to the rectum.



from conventional prostate adenocarcinoma. LCNEC constitutes large arranged cell in nests and these tumor cells have also abundant cytoplasm and vesicular nucleoli with high mitotic activity by histologic examination. As in our case, geographic necrosis is often observed and it's accepted as an important histologic finding of this tumor type. In the immunohistochemical examination, PNEC usually does not express and stain with common prostate adenocarcinoma markers such as AR, P501S, PSMA, and PSA. But, it expresses and shows characteristically positive staining with neuroendocrine markers like chromogranin A, CD56, NSE, and synaptophysin. Among these, synaptophysin is considered as the most sensitive biomarker for PNEC (5). In addition, cell proliferation assessed by the Ki-67 index is significantly associated with poor prognoses in patients with prostate cancer (6). Whereas Ki-67 index is usually under 10% for prostate adenocarcinoma, this score is expected to be high usually greater than 50% for PNEC (5-7). In our case, the Ki-67 proliferation index of tumor cells were 95% and tumor cells showed strong and diffusely positive staining with synaptophysin that supported the neuroendocrine origin of the malignant cells.

Neuroendocrine carcinoma of the prostate is often diagnosed in patients who received long-lasting ADT for the treatment of previous prostate adenocarcinoma. It's shown that histologically focal neuroendocrine differentiation is found in prostate adenocarcinomas treated by ADT ranging from 10% to 80% (8). Apart from this relationship between neuroendocrine morphology and ADT, primary PNEC is as yet only limited to a few case reports in the current literature. Only a case series was reported by Evans et al. that evaluated clinicopathologic features of 7 cases with LCNEC of the prostate. Six of these tumors arose from prostate adenocarcinoma that was previously treated with hormone therapy. Only one case had de-novo LCNEC of the prostate. Platinum-based systemic chemotherapy was chosen in all but one patient. The one with clinically confirmed organ-confined disease underwent radical cystoprostatectomy after TUR-P showed LCNEC. However, all patients in this series with complete follow-up lost their lives due to widespread dissemination of their tumors with a mean survival of seven months (3).

Patients with LCNEC are more likely to present with severe lower urinary obstruction. Serum PSA value may be normal especially patients with primary LCNEC. Therefore, these tumors are most frequently diagnosed in the advanced stage. It is shown that most common metastatic sites are bone, brain, lung, and liver. A PET-MR might be a more suitable way to provide accurate clinical staging. Several studies showed that PET-MR had excellent diagnostic performance for the overall detection of the malignancies due to higher soft-tissue contrast of MRI with the highly sensitive evaluation of metabolism and molecular processes of PET (9). In addition, one of the most important questions is which is the most suitable way for the treatment of a malignant ureteral obstruction in these patients. We recommend metallic tumor stents (Resonance®) since several studies have shown that the metallic stents are more resistant to extrinsic compression than their plastic counterparts (10).

Treatment alternatives for LCNEC of the prostate included radical cystoprostatectomy, systemic chemotherapy, and radiation therapy. Ho-

wever, no certain consensuses have been made about the most appropriate option due to the lack of high volume studies, yet. Systemic chemotherapy should be chosen including platinum-based chemotherapy as it determined before in the treatment of neuroendocrine tumor of the lung (11). It is not clear in the literature whether radical cystoprostatectomy provides long term cancer-specific survival for organ-confined disease or not. There is too little data about whether radiation therapy is effective in LCNEC or not, and these findings usually exist from lung cancer series (11, 12). Therefore, such challenging cases should be discussed in multidisciplinary team meetings and care must be individualized depending on the tumor stage.

The other important scientific observation of our case report is the dexamethasone-induced NDI. We excluded other potential causes of NDI. To our knowledge, this is the second case report related to this topic after the first description by Toftegaard et al. (13). Dexamethasone was given as a standard protocol in patients treated by SBRT. Animal studies have shown that there was negative feedback between glucocorticoids and the ADH-secretion from the neurohypophysis (14). However, evidence--based, high-quality studies are needed to learn the exact role of glucocorticoids on the kidneys.

In conclusion, we strongly recommend that LCNEC should be kept in mind when patients have a prostate which is abnormally large in size and cause bilateral hydroureteronephrosis due to invasion through the bladder neck and trigone. In addition, the physician should not forget that widespread utilization of the potent androgen receptor signaling inhibitors can cause a rise in the incidence of the PNEC. Though clinical findings can be helpful for LCNEC, differential diagnosis currently depends on histopathologic evaluation. Therefore, tissue sampling using transrectal ultrasound guided prostate biopsy or TUR-P should not be neglected whenever clinical features are suggestive of LCNEC even in patients with a normal PSA value as in our case.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. di Sant'Agnese PA, Cockett AT. Neuroendocrine differentiation in prostatic malignancy. Cancer. 1996;78:357-61.
2. Okoye E, Choi EK, Divatia M, Miles BJ, Ayala AG, Ro JY. De novo large cell neuroendocrine carcinoma of the prostate gland with pelvic lymph node metastasis: a case report with review of literature. Int J Clin Exp Pathol. 2014;7:9061-6.
3. Evans AJ, Humphrey PA, Belani J, van der Kwast TH, Srigley JR. Large cell neuroendocrine carcinoma of prostate: a clinicopathologic summary of 7 cases of a rare manifestation of advanced prostate cancer. Am J Surg Pathol. 2006;30:684-93.
4. Alanee S, Moore A, Nutt M, Holland B, Dynda D, El-Zawahry A, et al. Contemporary Incidence and Mortality Rates of Neuroendocrine Prostate Cancer. Anticancer Res. 2015;35:4145-50.
5. Parimi V, Goyal R, Poropatich K, Yang XJ. Neuroendocrine differentiation of prostate cancer: a review. Am J Clin Exp Urol. 2014;2:273-85.
6. Verhoven B, Yan Y, Ritter M, Khor LY, Hammond E, Jones C, et al. Ki-67 is an independent predictor of metastasis and cause-specific mortality for prostate cancer patients treated on Radiation Therapy Oncology Group (RTOG) 94-08. Int J Radiat Oncol Biol Phys. 2013;86:317-23.
7. Berney DM, Gopalan A, Kudahetti S, Fisher G, Ambroisine L, Foster CS, et al. Ki-67 and outcome in clinically localised prostate cancer: analysis of conservatively treated prostate cancer patients from the Trans-Atlantic Prostate Group study. Br J Cancer. 2009;100:888-93.
8. Epstein JI, Amin MB, Beltran H, Lotan TL, Mosquera JM, Reuter VE, et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. Am J Surg Pathol. 2014;38:756-67.
9. Shen G, Hu S, Liu B, Kuang A. Diagnostic Performance of Whole-Body PET/MRI for Detecting Malignancies in Cancer Patients: A Meta-Analysis. PLoS One. 2016;11:e0154497.
10. Abbasi A, Wyre HW, Ogan K. Use of full-length metallic stents in malignant ureteral obstruction. J Endourol. 2013;27:640-5.
11. Travis WD. Lung tumours with neuroendocrine differentiation. Eur J Cancer. 2009;45 Suppl 1:251-66.
12. Paci M, Cavazza A, Annessi V, Putrino I, Ferrari G, De Franco S, et al. Large cell neuroendocrine carcinoma of the lung: a 10-year clinicopathologic retrospective study. Ann Thorac Surg. 2004;77:1163-7.

13. Toftegaard M, Knudsen F. Massive vasopressin-resistant polyuria induced by dexamethasone. Intensive Care Med. 1995;21:238-40.
14. Raff H. Glucocorticoid inhibition of neurohypophysial vasopressin secretion. Am J Physiol. 1987;252(4 Pt 2):R635-44.

Correspondence address:
Cem Basatac, MD
Department of Urology,
Istanbul Bilim University, Istanbul, Turkey
Fax: + 90 212 272-3461
E-mail: cembasatac@gmail.com

ARTICLE INFO

Cem Basatac
http://orcid.org/0000-0002-5310-3359

Int Braz J Urol. 2020; 46: 859-63

Submitted for publication:
March 11, 2019

Accepted after revision:
May 06, 2019

Published as Ahead of Print:
August 01, 2019

VIDEO SECTION

Vol. 46 (5): 864-866, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2018.0154

Transvaginal repair of Neobladder Vaginal Fistula with Martius Flap

Daniela Carlos [1], Nitya Abraham [1], Tian C. Zhou 1, Michael Hung [1]

[1] *Montefiore Medical Center/Albert Einstein College of Medicine, NY, USA*

ABSTRACT

Introduction: Neobladder vaginal fistula (NVF) is a known complication after cystectomy and orthotopic diversion in women, occurring in 3-5% of women. Possible risk factors for fistula formation include compromised tissue vascularity due to surgical dissection and/or radiotherapy, suture line proximity, local tissue recurrence, and injury to the vaginal wall during dissection. The surgical repair of a NVF can be challenging secondary to vaginal shortening, atrophy, local inflammation from chronic exposure to urinary leakage, and the proximity of the neobladder to the anterior vaginal wall. In this video, we present transvaginal repair of a NVF with Martius flap interposition.

Materials and Methods: This is the case of a 47 year old woman with a history of radical cystectomy and creation of a Studer pouch secondary to bladder cancer two years prior who subsequently developed a NVF. Evaluation included an office cystoscopy which demonstrated a 3-4mm left-sided neobladder vaginal fistula at the level of the ileal-urethral anastomosis. No pelvic organ prolapse or evidence of bladder cancer recurrence was appreciated.

Results: A vaginal approach for the NVF repair was performed with a Martius flap interposition. A water-tight closure was achieved without any intraoperative or immediate postoperative complications. The urethral Foley was removed at 2 weeks and by 4 weeks the patient did not report any urinary leakage.

Conclusions: Neobladder vaginal fistula is a rare complication following cystectomy and orthotopic urinary diversion that can be repaired using a transvaginal approach. A Martius flap interposition is important to augment success of the repair. If a transvaginal approach fails a transabdominal approach or conversion to cutaneous diversion may be necessary.

INTRODUCTION

Radical cystectomy is recommended for localized or recurrent non-invasive bladder cancer in patients who are good surgical candidates. Subsequent urinary diversion consists of an ileal conduit or various reservoirs including an orthotopic neobladder that mimics the physiologic process of micturition (1, 2). The Studer orthotopic neobladder is created using a 60- to 65cm segment of terminal ileum reconstructed into a U-shaped reservoir which is connected proximally to the ureters and distally to the urethra. This type of diversion offers good functional outcomes without compromising oncologic control.

Neobladder vaginal fistula (NVF) is a known complication after cystectomy and orthotopic diversion in women, occurring in 3-5% of women (3, 4). Possible risk factors for fistula formation include compromised tissue vascularity due to surgical dissection and/or radiotherapy, suture line proximity, local tissue recurrence, and injury to the vaginal wall during dissection. The surgical repair of a NVF can be challenging secondary to vaginal shortening, atrophy, local inflammation from chronic exposure to urinary leakage, and the proximity of the neobladder to the anterior vaginal wall. In this video, we present transvaginal repair of a neobladder vaginal fistula with Martius flap interposition.

MATERIALS AND METHODS

This is the case of a 47 year old woman with a history of bladder cancer status post radical cystectomy, and creation of a Studer pouch two years prior who subsequently developed a neobladder vaginal fistula. She developed postoperative urinary incontinence within the first year requiring continuous pad usage with subsequent poor quality of life. She underwent a CT scan that did not demonstrate any pelvic recurrence or lymphadenopathy as well as an exam under anesthesia, cystoscopy, and pouchogram. Cystoscopy demonstrated a 3-4mm left-sided neobladder vaginal fistula at the level of the ileal-urethral anastomosis. No pelvic organ prolapse or evidence of bladder cancer recurrence was appreciated.

The procedure was begun by first performing a cystoscopy, identifying the fistulous tract, and placing a 10F Foley in order to be able to identify it throughout the case. The anterior vaginal wall was then infiltrated with lidocaine with epinephrine and an inverted U-shaped incision was made in the vaginal epithelium with the fistulous tract at the apex of the incision. The underlying vaginal epithelium was dissected off the muscularis circumferentially around the fistula. Once there was adequate mobilization around the fistula circumferentially, the fistula was closed with interrupted 4-0 PDS suture on RB-1 needle. After the bladder was closed, the muscularis was mobilized by sharp dissection in order to cover the incision while avoiding overlapping suture lines. A watertight closure was appreciated by distending the bladder with diluted methylene blue. A left Martius flap was harvested by making a vertical incision on the left labia majora and mobilizing the subcutaneous fat pad. The superior pedicle was divided leaving the inferior pedicle with adequate blood supply. The pedicle was then tunneled subcutaneously towards the vaginal incision and interposed over the vaginal muscularis to provide another layer of closure using interrupted 4-0 Vicryl® stitches. The vaginal epithelium was closed in a running-locked fashion with Vicryl® suture. Hemostasis was achieved at both vaginal and groin incisions. The groin incision was closed in a subcuticular fashion with 4-0 Monocryl. A Penrose drain was left within the subcutaneous space at the groin site. The following day the vaginal packing and Penrose were removed when drainage was no longer occurring.

RESULT

A vaginal approach for the NVF repair was performed with a Martius flap interposition. A water--tight, three layered closure was achieved without any intraoperative or immediate postoperative complications. After two weeks, the urethral Foley was removed and the patient reported no leakage from vagina. She developed retention requiring catheterization and only reported incontinence at night. At 4 weeks post-op the nighttime incontinence resolved after evening fluid restriction. She had no daytime incontinence. At 6 months follow-up the patient reported stress urinary incontinence 2-3 hours after catheterizing the bladder. She was offered urethral bulking agent injection but deferred at this time.

DISCUSSION

The risk of developing a NVF is estimated to be 3-5% of women who have undergone cystectomy and orthotopic diversion. In addition, after the creation of a neobladder, high rates of some form of voiding or storage dysfunction occur (5-8). Based on several functional outcome studies, 56-58. 0% of the patients require clean intermittent self-catheterization to facilitate bladder emptying. Stein et al. (9), reported frequent leakage or no urinary control whatsoever during daytime in 23% of women as well as nocturnal urinary incontinence reported by 34%. Even though functional complications appear to be common, compared to ileal conduits, women who have undergone neobladder diversion report improved quality of life due to better self--confidence as well as restoration of leisure and professional activities (8, 9). Since urinary incontinence can be an expected finding after a neobladder creation, a neobladder vaginal fistula must be ruled out in this clinical setting.

Given the distal location of the fistula at the level of the bladder neck and risk of abdominal adhesions from her neobladder surgery, we preferred a vaginal approach. In addition, she had no prior pelvic radiation and this was the first attempt at repairing the fistula, further supporting this approach. If the

vagina is not capacious, an episiotomy can be made to improve access to the fistula.

CONCLUSION

Neobladder vaginal fistula is a known complication following cystectomy and orthotopic urinary diversion that can be repaired using a transvaginal approach. A Martius flap interposition is important to augment success of the repair. If a transvaginal approach fails, a transabdominal approach or conversion to cutaneous diversion may be necessary (10).

Consent

Written informed consent was obtained from the patient for collection of data and publication of this Video article.

ABBREVIATIONS

NVF = neobladder vaginal fistula
BCG = Bacillus Calmette-Guérin

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Gakis G, Stenzl A, et al. (2010) Ileal neobladder and its variants. Eur Urol Suppl 9:745–53
2. Studer UE, Burkhard FC, Schumacher M, Kessler TM, Thoeny H, Fleischmann A, et al. Twenty years experience with an ileal orthotopic low pressure bladder substitute-lessons to be learned. J Urol. 2006;176:161-6.
3. Rapp DE, O'connor RC, Katz EE, Steinberg GD. Neobladder-vaginal fistula after cystectomy and orthotopic neobladder construction. BJU Int. 2004;94:1092-5; discussion 1095.
4. Kumar A, Das SK, Trivedi S, Dwivedi US, Singh PB. Neobladder vaginal fistula: an unusual complication after orthotopic urinary diversion. Saudi J Kidney Dis Transpl. 2009;20:658-61.
5. Jentzmik F, Schrader AJ, de Petriconi R, Hefty R, Mueller J, Doetterl J, et al. The ileal neobladder in female patients with bladder cancer: long-term clinical, functional, and oncological outcome. World J Urol. 2012;30:733-9.
6. Hobisch A, Tosun K, Kinzl J, Kemmler G, Bartsch G, Höltl L, et al. Life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. Semin Urol Oncol. 2001;19:18-23.
7. Ali-El-Dein B, Ashamallah A. Vaginal repair of pouch-vaginal fistula after orthotopic bladder substitution in women. Urology. 2013;81:198-202.
8. Granberg CF, Boorjian SA, Crispen PL, Tollefson MK, Farmer SA, Frank I, et al. Functional and oncological outcomes after orthotopic neobladder reconstruction in women. BJU Int. 2008;102:1551-5.
9. Stein JP, Penson DF, Lee C, Cai J, Miranda G, Skinner DG. Long-term oncological outcomes in women undergoing radical cystectomy and orthotopic diversion for bladder cancer. J Urol. 2009;181:2052-8.
10. Kumar A, Das SK, Trivedi S, Dwivedi US, Singh PB. Neobladder vaginal fistula: an unusual complication after orthotopic urinary diversion. Saudi J Kidney Dis Transpl. 2009;20:658-61.

ARTICLE INFO

Daniela Carlos
http://orcid.org/0000-0002-9964-7765

Available at: http://www.intbrazjurol.com.br/video-ection/20180154_Carlos_et_al
Int Braz J Urol. 2020; 46 (Video #19): 864-6

Submitted for publication:
March 10, 2019

Accepted after revision:
October 06, 2019

Published as Ahead of Print:
February 10, 2020

Correspondence address:
Daniela Carlos, MD
Business Address: 735 Ave Ponce de Leon 613
San Juan, PR 00917
Fax: +1 718-975-5443
E-mail: danielamcarlos@gmail.com

VIDEO SECTION

Vol. 46 (5): 867-867, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2018.0839

Transurethral resection of bladder tumor through artificial urinary sphincter

Kevin Heinsimer [1], Lucas Wiegand [2]

[1] USF Health Morsani College of Medicine-Urology,Tampa General Circle, Tampa, Florida, United States; [2] University of South Florida-Urology, Tampa General Circle, Tampa, Florida, United States

ABSTRACT

Artificial Urinary Sphincter (AUS) is a common treatment for stress urinary incontinence, especially in patients treated for prostate cancer. A small number of patients with an AUS will subsequently develop bladder cancer. These patients are especially hard to manage due to risk of cuff erosion with transurethral interventions. We present a case of an 81-year-old male, with history of prostatectomy and AUS placement, found to have a 2.5cm bladder tumor. He underwent transurethral resection of bladder tumor (TURBT) through a 5cm AUS cuff using a 16.5Fr flexible cystoscope and 3fr bugbee monopolar electrode. The tumor was able to be resected en-bloc. The patient's cuff was deactivated prior to TURBT and reactivated 72hr post-operatively. The patient experienced no complications or compromises from an oncologic or incontinence standpoint. Final pathology was spindle cell carcinoma without muscle invasion.

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Kevin Heinsimer
http://orcid.org/0000-0002-4400-0294

Available at: http://www.intbrazjurol.com.br/video-section/20180839_Heinsimer_et_al
Int Braz J Urol. 2020; 46 (Video #20): 867-867

Submitted for publication:
January 14, 2019

Accepted after revision:
May 04, 2019

Published as Ahead of Print:
July 15, 2019

Correspondence address:
Kevin Heinsimer, MD
Assistant Professor of Urology,
University of South Florida, 2 Tampa General Circle
Morsani College of Medicine
STC 6, Tampa, FL 33606, United States
E-mail: kheinsimer@health.usf.edu

VIDEO SECTION

Vol. 46 (5): 868-868, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0089

Urolift® with median lobe resection for trilobar BPH

Julio Slongo [1], Aram Loeb [1], Rafael E Carrion [1]

[1] *Department of Urology, University of South Florida, Tampa, FL, USA*

ABSTRACT

Introduction and Objective: Urolift® is a minimally invasive surgical treatment for men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). Currently, it is contraindicated in patients with a median lobe. With this video, we demonstrate an example of our initial experience with Urolift for patients with trilobar BPH.
Materials and Methods: JW, 67 years old male with a long history of LUTS, with an AUA-SS of 20. His symptoms were improved with Tamsulosin, but he did not tolerate retrograde ejaculation associated with it. Work-up included UA, PSA, prostate US (43 grams) and cystoscopy, which showed obstructing lateral lobes and a large median lobe. He was counseled on different options, and elected for the above procedure, citing his high concern for retrograde ejaculation and desire to be off medication.
Results: The surgery was performed in an outpatient setting, with no need for a Foley catheter. At one-month follow-up Tamsulosin was stopped, and the patient was experiencing voiding symptoms improvement. At three months he reported extreme satisfaction with the procedure. His AUA-SS improved by 30% off medications and he denied any sexual side effects.
Conclusions: Urolift® is a good treatment modality for patients with BPH, even in the presence of an obstructing median lobe- which can be easily addressed with a simple TUR. This video is an example of our initial experience, with short-term follow-up. More data and longer follow-up are needed, in the hope that with this video the indications of the procedure may be expanded- meeting the concern of many of our patients about sexual side effects caused by BPH treatment modalities.

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Julio Slongo
http://orcid.org/0000-0001-9895-6972

Available at: http://www.intbrazjurol.com.br/video-section/20190089_Slongo_et_al
Int Braz J Urol. 2020; 46 (Video #21): 868-868

Submitted for publication:
February 07, 2019

Accepted after revision:
October 06, 2019

Published as Ahead of Print:
December 30, 2019

Correspondence address:
Julio Slongo, MD
Department of Urology, University of South Florida
2 Tampa General Cir.
Tampa Florida 33620-9951, USA
Telephone: + 1 813 974-4115
E-mail: julioslongo@health.usf.edu

VIDEO SECTION

Vol. 46 (5): 869-869, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0336

Combined robotic radical prostatectomy and left partial nephrectomy by a single port approach

Rair Valero [1], Guilherme Sawczyn [1], Juan Garisto [1], Roger Yau [1], Jihad Kaouk [1]

[1] *Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio, USA*

ABSTRACT

Introduction: To present the first case of a concomitant robotic radical prostatectomy and a left robotic partial nephrectomy performed by a single-port approach using the SP® da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA).
Materials and Methods: A 66-year-old male diagnosed with localized prostate cancer and a left kidney renal mass incidentally found on computed tomography (CT) during prostate cancer evaluation. Procedures were performed using a single supra-umbilical 3cm incision, plus one additional laparoscopic port, utilizing a standard Gelpoint® (Applied Medical, Rancho Santa Margarita, CA) and replicating the technique previously described for single-port transperitoneal radical prostatectomy and partial nephrectomy with the use of the SP® robotic platform.
Results: Total operative time was 256 minutes (mins) with a console time of 108 mins for radical prostatectomy, and 101 mins for the partial nephrectomy respectively, including a warm ischemia time of 26 mins. Estimated blood loss was 250cc. Blood transfusion was not needed. Final pathology was adenocarcinoma of the prostate Gleason 4+3=7, pT3aN0R0 (9 pelvic lymph nodes negatives) and for the kidney renal cell carcinoma papillary type 1 pT1bNxR0. After two months of follow-up, PSA was undetectable and abdominopelvic CT scan did not showed any recurrence.
Conclusions: The single-port approach has advantage as easier surgical planning and transition for combined and multi-quadrants surgeries: faster recovery, minimal postoperative pain and need for opioids, and acceptable cosmetic outcomes.

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Rair J Valero C
http://orcid.org/0000-0002-7579-2845

Available at: http://www.intbrazjurol.com.br/video-section/20190336_Valero_et_al
Int Braz J Urol. 2020; 46 (Video #22): 869-869

Submitted for publication:
May 20, 2019

Accepted after revision:
September 24, 2019

Published as Ahead of Print:
December 30, 2019

Correspondence address:
Jihad Kaouk, MD
Glickman Urological and Kidney Institute
Cleveland Clinic, Cleveland, Ohio, USA
9500 Euclid Ave, Q-10
Cleveland, OH 44195, USA
Telephone: +1 216 444-2976
E-mail: kaoukj@ccf.org

VIDEO SECTION

Vol. 46 (5): 870-870, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0380

Giant escrotal hidradenitis suppurativa

Iris Coello [1], Javier Brugarolas [1], Mariano Rovira [1], Luis Ladaria [1], Carlos Aliaga [1], Enrique Carmelo Pieras [1]

[1] *Department of Urology, Hospital Universitario Son Espases, Palma de Mallorca, Illes Balears, Spain*

ABSTRACT

Scrotal lymphedema secondary to hidradenitis suppurativa is a very rare entity. We present a five-year evolution case that has been treated with several medical and surgical treatments with poor outcomes. In severe cases, surgical management is the treatment of choice to improve the patient's overall quality of life.
We perform a technique of total excision and use of free graft, with good aesthetic and functional results for the patient.

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Iris Coello
http://orcid.org/0000-0001-5711-1236

Available at: http://www.intbrazjurol.com.br/video-section/20190380_Coello_et_al
Int Braz J Urol. 2020; 46 (Video #23): 870-870

Submitted for publication:
June 12, 2019

Accepted after revision:
October 22, 2019

Published as Ahead of Print:
December 30, 2019

Correspondence address:
Iris Coello Torà, MD
Department of Urology
Hospital Universitario Son Espases
Ctra / Valldemossa 79,
07120, Palma de Mallorca, Spain
E-mail: siricoto@gmail.com

VIDEO SECTION

Vol. 46 (5): 871-872, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.0059

How far is too far? Exploring the indications for robotic partial nephrectomy in a highly complex kidney tumor

Andrea Minervini [1], Antonio Andrea Grosso [1], Fabrizio Di Maida [1], Andrea Mari [1], Gianni Vittori [1], Gianluca Muto [1], Marco Carini [1]

[1] *Department of Oncologic, Minimally-Invasive Urology and Andrology, Careggi Hospital, University of Florence, Italy*

ABSTRACT

Purpose: The conservative management of localized renal masses has been recently widened to cT2 tumors showing encouraging functional and oncological outcomes (1). This video aims to report the conservative management of a highly complex renal tumor treated with robotic pure enucleation in our center, specifically focusing on preoperative work-up, video-reported surgical steps and perioperative outcomes.

Materials and Methods: A 63 year-old lady underwent CT scan revealing a single 75 x 68mm, mainly endophytic, right renal mass dislocating the vascular pedicle (cT3a). Two renal arteries and two veins were identified. PADUA, RENAL and simplified SPARE scores were 14a, 12a and 12 respectively. Since the contralateral kidney was hypotrophic, the indication for nephron-sparing approach was considered absolute. Preoperative surgical planning included the employment of 3D-virtual models (2).

Results: Operative time was 150 minutes and warm ischemia time was 25 minutes. No major complication occurred. Histopathological analysis revealed a cromophobe renal cell carcinoma with extension to perirenal fat tissue (pT3a). Resection technique was classified as pure enucleation since Surface-Intermediate-Base (SIB) score was 0-0-0 (3, 4). At seven-months follow-up no signs of local or systemic recurrence were recorded. Postoperative CT-scan revealed optimal parenchymal volume preservation with last creatinine blood level of 1.16mg/dL.

Conclusion: This video highlights how, in experienced hands, robotic partial nephrectomy represents a feasible, effective treatment option for surgical management of highly complex renal tumors. The employment of intraoperative ultrasonography and 3D-virtual models allowed to accurately tailor surgical approach, improving the perception of tumor anatomy and its vascularization and maximizing perioperative outcomes.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bertolo R, Autorino R, Simone G, Derweesh I, Garisto JD, Minervini A, et al. Outcomes of Robot-assisted Partial Nephrectomy for Clinical T2 Renal Tumors: A Multicenter Analysis (ROSULA Collaborative Group). Eur Urol. 2018;74:226-32.
2. Checcucci E, Amparore D, Pecoraro A, Peretti D, Aimar R, De Cillis S, et al. 3D mixed reality holograms for preoperative surgical planning of nephron-sparing surgery: evaluation of surgeons' perception. Minerva Urol Nefrol. 2019. 5 ahead of print.
3. Minervini A, Carini M, Uzzo RG, Campi R, Smaldone MC, Kutikov A. Standardized reporting of resection technique during nephron-sparing surgery: the surface-intermediate-base margin score. Eur Urol. 2014;66:803-5.
4. Minervini A, Campi R, Kutikov A, Montagnani I, Sessa F, Serni S, et al. Histopathological Validation of the Surface-Intermediate-Base Margin Score for Standardized Reporting of Resection Technique during Nephron Sparing Surgery. J Urol. 2015;194:916-22.

Correspondence address:
Antonio Andrea Grosso, MD
Department of Oncologic, Minimally-Invasive Urology and Andrology, Careggi Hospital
University of Florence,
Largo Brambilla, 3-50134, Florence (Italy)
Telephone: +39 39 2097-8948
E-mail: grossoantonioandrea@gmail.com

Submitted for publication:
January 29, 2020

Accepted after revision:
February 26, 2020

Published as Ahead of Print:
May 25, 2020

ARTICLE INFO

Antonio Andrea Grosso
https://orcid.org/0000-0001-5973-789X

Available at: http://www.intbrazjurol.com.br/video-section/20190059_Minervini_et_al
Int Braz J Urol. 2020; 46 (Video #24): 871-2

LETTER TO THE EDITOR

Vol. 46 (5): 873-874, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.0103

Re: Predictive and prognostic impact of preoperative complete blood count based systemic inflammatory markers in testicular cancer

Cengiz Beyan [1], Esin Beyan [2]

[1] Department of Hematology, Ufuk University Faculty of Medicine, Ankara, Turkey; [2] Department of Internal Medicine, University of Health Sciences, Kecioren Training and Research Hospital, Ankara, Turkey

To the editor,

We read with great interest the retrospective research of Arda et al. about the predictive and prognostic impact of some parameters based on complete blood count in patients with testicular cancer (1). The researchers suggested that some parameters such as neutrophil lymphocyte ratio (NLR), mean platelet volume (MPV) and red cell distribution width (RDW) could provide predictive and prognostic information in these patients. We would like to emphasize the factors that may have affected incorrectly some of the parameters evaluated in this study.

First, this study included retrospective data from two different centers of a very broad period of 10 years. Unlike prospective studies, it is not possible to reduce pre-analytical and analytical errors in retrospective studies.

MPV is a parameter which measurement methodology has not been standardized, which is significantly affected by epidemiological factors such as age, gender, race and variations in the measurement method (2). The age difference between the patient and the control group was a factor that may have affected the results in this study. It has been shown that the variability of the time elapsed from the venipuncture to the measurement time cause to deviations of 2-50% in the MPV results (3, 4). In addition, different technologies used for complete blood count also lead to deviations in results (4-6). MPV measurement times and devices used for MPV measurement were unknown in this study. All these factors make the MPV data of the study unreliable. The preoperative MPV cut-off value specified in Table 3 was probably incorrectly written, and actually, the fact that MPV measurement still could not been standardized today, it makes impossible to determine a cut-off value for MPV.

In the study, only lymphocyte and neutrophil percentages were used in comparisons and absolute lymphocyte and absolute neutrophil numbers were not specified. Since the white blood cell values of the cases are unknown and absolute lymphocyte and neutrophil numbers are not given, it remains to be not understood whether the statistical difference in the percentage of lymphocytes and neutrophils is a real difference between the patient and control groups. Moreover, the age difference between the patient and control groups was also statistically significant, and this was a condition that might have affected the results, as the absolute lymphocyte counts decrease with increasing age (7, 8).

It is stated in the discussion section that especially NLR and RDW can be used as predictive and prognostic factor with the highest sensitivity and specificity in patients with testicular cancer. However, in Table 4, where NLR 1.78 was used as the cut-off value, the fact that RDW values were not different between the groups with high and low NLR was a situation that did not support this statement.

As a result, some parameters based on complete blood count may have no predictive and prognostic impact in patients with testicular cancer.

LIST OF ABBREVIATIONS

MPV = mean platelet volume
NLR = neutrophil lymphocyte ratio
RDW = red cell distribution width

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Arda E, Arikan G, Akdere H, Akgul M, Yuksel I. Predictive and prognostic impact of preoperative complete blood count based systemic inflammatory markers in testicular cancer. Int Braz J Urol. 2020;46:216-23.
2. Noris P, Melazzini F, Balduini CL. New roles for mean platelet volume measurement in the clinical practice? Platelets. 2016;27:607-12.
3. Jackson SR, Carter JM. Platelet volume: laboratory measurement and clinical application. Blood Rev. 1993;7:104-13.
4. Beyan C, Beyan E. Were the measurements standardized sufficiently in published studies about mean platelet volume? Blood Coagul Fibrinolysis. 2017;28:234-6.
5. Lippi G, Pavesi F, Pipitone S. Evaluation of mean platelet volume with four hematological analyzers: harmonization is still an unresolved issue. Blood Coagul Fibrinolysis. 2015;26:235-7.
6. Latger-Cannard V, Hoarau M, Salignac S, Baumgart D, Nurden P, Lecompte T. Mean platelet volume: comparison of three analysers towards standardization of platelet morphological phenotype. Int J Lab Hematol. 2012;34:300-10.
7. MacKinney AA Jr. Effect of aging on the peripheral blood lymphocyte count. J Gerontol. 1978;33:213-6.
8. Valiathan R, Ashman M, Asthana D. Effects of Ageing on the Immune System: Infants to Elderly. Scand J Immunol. 2016;83:255-66.

Correspondence address:
Cengiz Beyan, MD, Prof.
Department of Hematology
Ufuk University Faculty of Medicine,
Çankaya, 06830, Ankara, Turkey
Telephone.: + 90 537 335-6542
E-mail: cengizbeyan@hotmail.com

ARTICLE INFO

Cengiz Beyan
https://orcid.org/0000-0003-1716-539X

Int Braz J Urol. 2020; 46: 873-4

Submitted for publication:
February 12, 2020

Accepted:
March 12, 2020

Published as Ahead of Print:
May 25, 2020

LETTER TO THE EDITOR

Vol. 46 (5): 875-876, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.0282

The old-style public health measures and the novel coronavirus outbreak

Antonio Cassio Assis Pellizzon [1]

[1] *Departamento de Oncologia Radiológica, Centro de Câncer AC Camargo, São Paulo, SP, Brasil*

To the editor,

Quarantines and travel bans have been the first response of Public Health against new infectious diseases. In health practice the quarantine refers to the separation of persons or communities who are exposed to an infectious disease. Isolation, in contrast, applies to the "separation" of persons who are known to be infected. Of importance is that isolation and quarantine can be imposed by law or voluntary. However, these classical public health measures are usually of limited utility for highly transmissible diseases. Other tools that Public Health have at hand are social distancing and community containment. The primary goal of such measures is to prevent person-to-person spread of disease, trying to interrupt transmission.

China has been preparing to contain future pandemics by applying lessons learnt from the SARS outbreak in 2003 (1). But public health measures taken at that time were successful for SARS because the vast majority of contaminated patients were symptomatic, thus identifiable and could be isolated. Delays in detection of infected patients may be related to subclinical symptoms and diverse initial manifestations in this new pandemy. Better assessments of viral shedding are needed to our understanding of the transmission dynamic and infection-control practices.

Early detection of Covid-19 is difficult because of its apparent subclinical nature in some persons (2). Although asymptomatic transmission has been suggested, it is uncertain if or when patients infected with SARS-CoV-2 initiate transmissions. Early data suggest that SARS-CoV-2 infection has higher estimated reproductive number (2.2 vs. 0.9) and a shorter estimated serial interval distribution (7.5 days vs. 12.6 days) when compared to MERS-CoV infection that occurred in 2015 (3, 4).

Whether these rigorous measures will result in victory depends on many factors (1): What is the proportion of subclinical disease that will never turn to symptomatic or mildly symptomatic, hence not be identified and isolated? (2). For infected persons what day is the peak viral shedding? (3). Does viral shedding occur before onset of symptoms? (4). Is there any other form of viral shedding?

The answers to all these and other questions will certainly drive the needed responses.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Zhong NS, Zeng GQ. Pandemic planning in China: applying lessons from severe acute respiratory syndrome. Respirology. 2008;13(Suppl 1):S33-5.
2. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med. 2020;382:970-1.
3. Cowling BJ, Park M, Fang VJ, Wu P, Leung GM, Wu JT. Preliminary epidemiological assessment of MERS-CoV outbreak in South Korea, May to June 2015. Euro Surveill. 2015;20:7-13. Erratum in: Euro Surveill. 2015;20(26).
4. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382:1199-207.

Correspondence address:
Antonio Cassio Assis Pellizzon, MD
Departamento de Oncologia Radiológica
Centro de Câncer AC Camargo,
Prof. Antonio Prudente, 211, Liberdade
São Paulo, SP, 01509-020, Brasil
Fax: + 55 11 2189-5101
E-mail: acapellizzon@accamargo.org.br

ARTICLE INFO

ACA Pellizzon
https://orcid.org/0000-0002-2083-5545

Int Braz J Urol. 2020; 46: 875-6

Submitted for publication:
April 09, 2020

Accepted:
April 13, 2020

Published as Ahead of Print:
May 25, 2020

LETTER TO THE EDITOR

Vol. 46 (5): 877-878, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.0297

REPLY BY THE AUTHORS: Comment on Polygamy, Sexual Behavior in a Population Under Risk for Prostate Cancer Diagnostic: An Observational Study From the Black Sea Region in Turkey

Abdullah Cirakoglu [1], Erdal Benli [1], Ahmet Yuce [1]

[1] Department of Urology, Ordu University, Faculty of Medicine, Ordu, Turkey

To the editor,

We thank Özkidik et al. for their interest and for their letter to the Editor (1). I will try to answer the questions they raised.

The authors do not think it is possible for all patients to have similar lifestyles and nutritional habits. It is only possible to ensure all conditions are equal with animal studies. In animal model studies, animals are housed in cages in the same place, fed with the same feed and water, creating an ideal environment. However, when working with humans, such an implementation does not comply with the reality of life. As stated in our paper, our region receives nearly no migration from other areas. Most people in the region have lived here for at least three generations. The culture, lifestyle and nutritional habits have been shaped by the climatic conditions, plant cover and geographic structure of the region. As this is not a place where people from different cultures migrate and live together like in metropolitan areas, the lifestyles and nutritional habits of people in the region are naturally similar. It is not possible to perform a study similar to animal models, but our region is close to ideal due to similar lifestyles and nutritional habits in the region.

The authors report it will be beneficial to state previous urethritis and prostatitis attacks. It should not be forgotten that urethritis and prostatitis are not diseases that always provide clinical findings. The PCPT study identified inflammation in 52.1% of samples from patients with biopsy performed (2). Similarly, some sexually transmitted diseases may be asymptomatic and therefore underreported (3). These infectious agents may maintain their presence latently especially in women. Similarly, they may not always cause clinical symptoms in males but may remain latent. As a result, the number of prostatitis and urethritis attacks patients suffered will not reflect the true infection rates. On the other hand, our study was not a study designed to reveal the cause-outcome relationship. It is an observational study. The results of our study identified that those with higher partner numbers had higher incidence of prostate cancer. The reason for this may be previous urethritis and prostatitis attacks, just as there may be other causes. It is necessary to design different studies to reveal the cause-outcome correlations about this topic.

There is no consensus in the literature about whether ejaculation frequency is effective on the development of prostate cancer or not. It is very difficult to determine a clear result about this topic. Prostate cancer development involves a long process. There are many factors affecting the frequency of ejaculation such as religious beliefs, environmental factors, health problems, etc. Similarly, even if people are married, their frequency of monthly sexual relations is variable. It is not possible to find definite numbers for this topic. All numbers given are subjective and there is always an error rate. To reveal clear information about this topic, it is necessary to monitor the study group for years, and record monthly ejaculation frequencies at certain intervals. In fact, even at the end of such a study, no definite evidence may be reached due to uncertainty about the effects of other factors. It is possible that the reason for uncertainty in the literature is due to this.

Additionally, as our study group was not monitored for years, it is not possible to clearly provide numbers about the monthly number of sexual relations for any year. As we state in the text, this data was obtained from patients when they came to the clinic. In our country, the beginning of regular sexual relations generally occurs with marriage. As the marital age of people is very variable, it is not possible to make an objective assessment by accepting a certain age limit. Additionally, the reliability of information given may be lower. The mean age in our patient group was nearly 65 years. When we asked these patients about their monthly sexual relations frequency from 20-30 years, from 30-40 years and from 40-50 years ago, their responses will have lower reliability. Information given about younger years and the present period will be subjective when answers are grouped according to age, but we think that responses when asked about relation frequency in youth and at present will be closer to the reality.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Özkidik M, Ibrahimov A. Comment on 'polygamy, sexual behavior in a population under risk for prostate cancer diagnostic: an observational study from the black sea region in Turkey'. Int Braz J Urol. 2018;44:1275-6.
2. Gurel B, Lucia MS, Thompson IM Jr, Goodman PJ, Tangen CM, Kristal AR, et al. Chronic inflammation in benign prostate tissue is associated with high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2014;23:847-56.
3. Decker CF. Sexually transmitted diseases: An overview. Dis Mon. 2016;62:258-9.

Correspondence address:
Abdullah Cirakoglu, MD
Department of Urology,
Faculty of Medicine, Ordu University
Ordu, Turkey
Phone: + 90 532 7169115
E-mail: dr_cirakoglu@yahoo.com

ARTICLE INFO

abdullah çırakoğlu
https://orcid.org/0000-0002-8602-5836

Int Braz J Urol. 2020; 46: 877-8

Submitted for publication:
April 18, 2020

Accepted:
May 05, 2020

Published as Ahead of Print:
May 25, 2020

LETTER TO THE EDITOR

Vol. 46 (5): 879-882, September - October, 2020
doi: 10.1590/S1677-5538.IBJU.2020.0316

The urologist's role in the fight of COVID-19 pandemic: mandatory mindset shift on the frontline

Alexandre Iscaife [1], Giovanni S. Marchini [1], Victor Srougi [1], Fabio C. M. Torricelli [1], Alexandre Danilovic [1], Fabio C. Vicentini [1], Marcos Machado [1], Marcelo Hisano [1], Bruno C. Tiseo [1], Júlio C. Bissoli [1], Marcello Cocuzza [1], Jorge Hallak [1], Miguel Srougi [1], William C. Nahas [1]

[1] *Divisão de Urologia, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, SP, Brasil*

To the editor,

Early in January 2020, we were living our regular lives. We are urologists at the "Hospital das Clínicas", University of Sao Paulo Medical School Clinical Hospital (HC-FMUSP), a 900-bed tertiary care facility inside an even wider and stronger health complex of 2.300 beds. Our Institution is responsible for about 350 highly complex monthly urological surgeries comprising all subspecialties in the field. We are inserted in the SUS (Sistema Único de Saúde), a unified health system with universal coverage created in 1990 (1). By the end of January 2020, we were attending crowded outpatient ambulatories, performing our usual surgeries, participating in the teaching of undergraduate students, teaching general surgery and urology residents, presenting scientific research in national and international scientific meetings.

When the press released the first confirmed case of corona virus disease (COVID-19) in late December, 2019 by the previously named "Wuhan virus" (Hubei province in China), later renamed as SARS-CoV-2 (2), not even the most pessimistic of us could imagine the impact it would have on our lives. Not even when it was spotted that the virus spread was hidden from the World and that doctors who tried to disseminate the information out died of the disease. At worst, if the virus crossed oceans and continents to our country, the routine of clinicians working in emergency rooms and intensive care units could be affected. Important and influential individuals of our national medical and political society came to the public warning that there was nothing to fear or to worry about. They told, we believed.

Those who lived to see April 2020 realized how naive we had been. Italy fell and the whole World kneeled together with the Mediterranean country. "No man is an island, entire of itself; every man is a piece of the continent, a part of the main. If a clod be washed away by the sea, Europe is the less" (3). How can the wisdom of a 17th century man be so contemporary?

Perhaps because true wisdom is beyond time. While Italy was bleeding, here in Brazil most of our surgeries started to be postponed and the outpatient clinics to be rescheduled based on international and national urological societies recommendations (4). Academic meetings were canceled indefinitely. One by one, all the familiar aspects of our lives were taken away from us. Whilst we could still get together in the cafes, we were astonished. What´s next?

Heartbreaking videos came from all over the World: first Italy, then Spain, England, and finally the United States. Great nations with robust health care systems took a hit like they have never seen before, at least not since the World War II. The context of a locally Chinese isolated crisis was rapidly dissipated into thin air. Thunders of war were quickly moving in our direction. It was real, surreal, and we did not plan for it. On March 24, the state of Sao Paulo officially announced social isolation. Cancelation of all sports events. Empty streets. Parks with closed gates. Children and parents trapped at home. We lost freedom as we knew it.

On April 7, our institution determined the reorganization of our facilities and the mandatory internal social distancing. We could no longer meet at the cafes. Our hospital, the largest in Latin America, initiated a war operation to receive patients with COVID-19 from all over the state. One building, 900 beds, and our greatest specialists of internal and intensive care medicine, pneumology, infectious diseases and anesthesiology were assigned to assist patients who were arriving by the dozens. The number of intensive care unit beds doubled and were immediately filled. All residents of all specialties were assigned to take care of these patients. Surgical and clinical specialties not related to COVID-19 were moved to other facilities within the complex. A significant reduction in all personnel daily activities to what was strictly essential, keeping an eye in the upcoming tsunami. Potential shortage of resources, tests and support equipment started to be of concern, irrespective of having the monetary funds or not, as an international hidden cold war was on the way to get vital equipment first. Chairmen from all departments and medical specialties managed to coordinate private donations from all over the country. Large companies, banks, financial institutions, and even middle-class citizens gave significant amounts of capital to support the hospital in a severe calamity like the one to come.

Whatever our thoughts were regarding the validity and effectiveness of social distancing, total quarantine was imposed. At that point, a feeling of uncertainty was in the air (5). Where should we go now? How do we continue to treat our patients? However, that specialist-based thinking that was still with us was about to change. The first mentality shift was about to take place. Inside our hospital all fit for the battle were selected to work in the coronavirus area. Irrespective of their initial status or division. There was no intermediate position anymore: you were either considered a COVID doctor, or a COVID-free doctor. There was no turning back. The Urology Division was asked to help further. In addition to providing the 40 beds of the ward, a group of urologists was assigned to participate in the direct care of patients with COVID-19 infection. We should lead a team of residents that included those from urology, under direct supervision of a clinician. We all remember the exact moment we received the call that gave us the assignment. There was not much time for us to question the reality: it was because they needed it, and because they trusted us. A given task is an accomplished mission. That is our nature as urologists. The "Hippocratic Oath" spoke louder within our souls.

After the first shock, we aimed for objectivity. Okay, how are we going to do that? A WhatsApp group was created and sharing of relevant information began. Institutional protocol for the diagnosis and treatment of COVID-19, the main publications in the area, podcasts, videos, preparation courses. Appropriate vestment? We already know how to do surgical dress up. But do we really? It is in the removal of the vestment that most of us become contaminated. Ok then, vestment removal courses: check! Intubation course with rapid sequence, indication of correct sedatives, neuromuscular blockers, no manual ventilation, mechanical ventilation, etc. Each hour that approached us of the first shift made evident how far we were from the internal medicine and advanced clinical care management. Anxiety was second to the strict sense of duty as physicians. Everyone had heard of someone without comorbidities as young as us who needed mechanical ventilation. Deadly virus, especially for the old ones. Fear grew. How would we protect our families from ourselves? Once responsible for our children, parents and significant others, now we had become a threat. Should we leave our homes? Who will look after them for us? A feeling of impotence rose. The kind of thrill we are not used to anymore.

The day before the first shift, insecurity: we had been urologists for so long, super specialists, how would it be practicing internal medicine again? Fifteen or more years ago, each one of us, for an intimate and individual reason, made a choice for the profession of faith within medicine: we would be urologists. Our main strength was this after all. And it would be as urologists that we would face this aberrant situation. Without realizing it, when we confronted the problem dispassionately, we were already being the urologists that we always were. Let the battle begin.

On the first shift, the ritual of dressing up and the look of the residents was uncomfortable: in their eyes, our same many fears as looking into a mirror of our soul. But they were younger. And we, in distress, were the reference. The only thing to do in such scenario: start working. With one relief, the colleague from the internal medicine was there. We had been fundamentally independent for so long that a peculiar former mood started to take place. We had our masters, of course, but part of the wisdom of those figures necessary for our professional autonomy was already introjected into us. We recalled the most primordial learning processes and remembered the relief that our teachers brought to the operating field when we lost the surgical plan or there was too much blood on it.

A reunion with humbleness, while still being practical: what could we offer residents and patients? We got accustomed to precision and only accept nothing less than highly successful results with fewer complications each year. Potency and continency after radical prostatectomies; microsurgical varicocele repairs and vasectomy reversals precisely and artistically performed, ureteral and kidney stones removed without incisions. We are strongly connected to the quality of life of men who come to us, trying to help to urinate better, to improve sexual function and to become fathers. We are also patient when we wait for children with urological diseases to reach the appropriate age for surgery, often more than once. When we obey countless steps for the safe resection of cancer. And we aim to invade the patient as little as possible, applying robotic and laparoscopic techniques. Finally, if the cure is not possible, we know how to alleviate symptoms and we know how to support the patients when they need us the most. As urologists, we use cutting edge techniques combined with humanism, practicing Medicine at its best.

It was like urologists that we entered that ward. And that's how we were able to point out and support the patients who were on their way home and those who needed more care. That's how we called the rapid response team to timely assist intubation and to transfer the patients to the intensive care unit before a critical situation emerged. That's how we discussed the compassionate use of antivirals and several drugs. That's how we were able to refine treatments and standardize patient care. That's how we brought human values to our institution, providing not only improvement in the care of our ward but also the remainder of the hospital. That's how we could understand that all the dystopia we were experiencing could be small in the broader view of a lifetime. It was as urologists that with the colleagues of the internal medicine, day by day, we found the best therapeutic proposals for our patients. And as urologists we suffer when the first colleague of the team and then the first resident of urology was struck by COVID-19. Thus, we prayed for them to reunite with us the soonest, healthy, to keep assisting our patients. Until they don´t need us anymore.

Leaving our comfort zone reminded us that true resistance comes from resilience. We must not forget that even the best genetic characteristics are vulnerable to chance. How many will not have disappeared in a great storm, or under a meteor, before they are even selected? We don't know when and how it all will end, but our commitment is to what we can do now. We were trained to practice a patient-centered medical approach. Each individual we treat is a singular person and deserves the best management for the situation that he or she is facing at that moment. We are now entering a time in which we may need to change our patient-centered to a population-centered mentality. This kind of mindset shift is so disruptive that it must be avoided and postponed if possible not to collide with our principles as doctors and human beings. We will not allow chance to destroy our best characteristics. We urologists, human beings, can give transcendence to everything we are experiencing. And that is what we will continue to do.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Castro MC, Massuda A, Almeida G, Menezes-Filho NA, Andrade MV, de Souza Noronha KVM, et al. Brazil's unified health system: the first 30 years and prospects for the future. Lancet. 2019;394:345-356.
2. [No Authors]. Naming the coronavirus disease (COVID-19) and the virus that causes it. Available at <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it>, accessed february 11, 2020.
3. Donne J: Devotions Upon Emergent Occasions. New York, Oxford University Press. 1987; Meditation 17.
4. Carneiro A, Wroclawski ML, Nahar B, Soares A, Cardoso AP, Kim NJ, Carvalho FT. Impact of the COVID-19 Pandemic on the Urologist's clinical practice in Brazil: a management guideline proposal for low- and middle-income countries during the crisis period. Int Braz J Urol. 2020;46:501-10.
5. Sampaio FJB. Reflections on the COVID-19 Pandemic. Int Braz J Urol. 2020;46:499-500.

Correspondence address:
Fabio C. M. Torricelli, MD
Rua Barata Ribeiro, nº 380 / 74
São Paulo, SP, 01308-000, Brasil
Telefone: + 55 11 27684552
E-mail: fabio.torricelli@hotmail.com

ARTICLE INFO

Torricelli FC
http://orcid.org/0000-0002-5845-0894

Int Braz J Urol. 2020; 46: 879-82

Submitted for publication:
April 19, 2020

Accepted:
April 20, 2020

Published as Ahead of Print:
May 05, 2020

INTERNATIONAL
BRAZ J UROL

INFORMATION FOR AUTHORS

Manuscripts submitted for publication should be sent to:

Luciano A. Favorito, MD, PhD
Editor, International Braz J Urol

Submit your article here:
https://www.intbrazjurol.com.br

Manuscripts must be written in current English or Portuguese. Non-native English speakers should ask a native specialist in medical English for checking the grammar and style. Either American or British English may be used but should be consistent throughout the manuscript.

A submission letter signed by all authors must accompany each manuscript. This letter must state that: a)- the paper or portion thereof have not been previously published and are not under consideration by another Journal, b)- that all authors have contributed to the information or material submitted for publication, and that all authors have read and approved the manuscript, c)- that the authors have no direct or indirect commercial financial incentive associated with publishing the manuscript, d)- that the source of extra-institutional funding, specially that provided by commercial companies, is indicated, e)- that the study had been reviewed and approved by a certified Ethical Board or Committee, including the nmeber of the approval dociment and the date of the approval, f)- a non-plagiarism statement (I (We) declare that all material in this assignment is my (our) own work and does not involve plagiarism). g)- Clinical trials must be registered on any Clinical Trials Registry and the letter must bring the number of registration and the name of the registry. After accepted for publication, the manuscript will become property of the **International Braz J Urol.**

Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, must be clearly disclosed when submitting a manuscript for review. If accepted, a disclosure will be published in the final manuscript.

The requirements for authorship and the general rules for preparation of manuscripts submitted to the **International Braz J Urol** are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med, 126: 36-47, 1997). An electronic version of the Uniform Requirements is available on various websites, including the International Committee of Medical Journal Editors web site: www.icmje.org.

In response to the concerns of the editors of scientific medical journals with ethics, quality and seriousness of published articles, a Committee on Publication Ethics (COPE) was established in 1997 and a guideline document was published. The International Braz J Urol signed, approved, and follows the COPE guidelines. The Editor strongly encourages the authors to carefully read these guidelines before submitting a manuscript **(www.publicationethics.org.uk/guidelines or www.brazjurol.com.br**, vol. 26 (1): 4-10, 2000).

Peer Review – All submissions are subject to editorial review. Typically, each manuscript is anonymously forwarded by the Editor to 4 Reviewers (at least 2). If the Editor receives conflicting or inconclusive revisions, the manuscript is always sent to 1 or 2 additional Reviewers before the Editor's decision. If considered necessary by the Editor or by the Reviewers, statistical procedures included in the manuscript will be analyzed by a statistician.

The **International Braz J Urol** contains six sections: **Original Article, Review Article, Surgical Technique, Challenging Clinical Case, Radiology Page**

and **Video Section**. The articles should be written in Portuguese or English official orthography.

Abbreviations should be avoided, and when necessary must be specified when first time mentioned. Unusual expressions may not be used. A list of abbreviations must be provided at the end of the manuscript.

Every manuscript submitted to publication should have a cover page containing the title, short title (up to 50 characters), authors and institution. Up to six key words should be provided. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine **(http://www.nlm.nih.gov/mesh/meshhome.html)**. One of the authors should be designated as correspondent and the complete correspondence address, telephone and fax numbers and E-mail should be provided.

If any financial support has been provided, the name of the institution should be mentioned.

Original Article: Original articles should contain a Cover Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusions, References, Tables and Legends, each section beginning in a separate page and numbered consecutively. Original articles should cover contemporary aspects of Urology or experimental studies on Basic Sciences applied to urology. The manuscript text should contain no more than 2500 words, excluding the Abstract. The number of authors is limited to five. References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

Review Article: Review articles are accepted for publication upon Editorial Board's request in most of the cases. A Review Article is a critical and systematic analysis of the most recent published manuscripts dealing with a urological topic. A State of the Art article is the view and experience of a recognized expert in the topic. An abstract must be provided.

Surgical Technique: These manuscripts should present new surgical techniques or instruments and should contain Introduction, Surgical Technique, Comments and up to five References. An abstract must be provided. At least five cases performed with the technique must be included.

Challenging Clinical Case: These manuscripts should present relevant clinical or surgical situations which can bring or consolidate our understanding of genesis, natural history, pathophysiology and treatment of diseases. *Structure of the articles*

Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario:** Description of case(s) relevant preceding and existing aspects;
- **Case(s) hypothesis and rational:** precepts, clinical and basic reasoning supporting the case(s) hypothesis and the raised scenario. Why is it important and is being reported?
- **Discussion and future perspectives:** what might it add and how does it relate to the current literature. 'Take-home message' - lessons learnt;
- **Table and/or Figure limits:** 2 (plates aggregating multiple images are encouraged) each exceeding table or figure will decrease 250 words of the full text;
- **Number of references:** 10-15.

Radiology Page: Will be published upon the Section Editor decision.

Video Section: The material must be submitted in the appropriate local, in the Journal's site, whe-

re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

ILLUSTRATIONS:

The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

ELECTRONIC SUBMISSION:

1) Do not embed the figures in the text, but supply them as separate files.
2) For Submitting Photographs Electronically, please:
Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, **not embed in Word or PowerPoint.**
3) For Submitting Line Artwork Electronically please note that:
Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
4) IMPORTANT - Avoid - Do Not

a) **DO NOT** embed the images in the text; save them as a separate file
b) **DO NOT** supply artwork as a native file. Most illustration packages now give the option to "save as" or export as EPS, TIFF or JPG.
c) **DO NOT** supply photographs in PowerPoint or Word. In general, the files supplied in these formats are at low resolution (less than 300 dpi) and unsuitable for publication.
d) **DO NOT** use line weights of less than 0.25 point to create line drawings, because they will nor appear when printed.

TABLES: The tables should be numbered with Arabic numerals. Each table should be typed on a single page, and a legend should be provided for each table. Number tables consecutively and cites each table in text in consecutive order.
REFERENCES: The References should be numbered following the sequence that they are mentioned in the text. The references should not be alphabetized. They must be identified in the text with Arabic numerals in parenthesis. Do not include unpublished material and personal communications in the reference list. If necessary, mention these in the body of the text. For abbreviations of journal names refer to the "List of Journals Indexed in Index Medicus" (http://www.nlm.nih.gov). The authors must present the references according to the following examples; the names of **all authors** must be included; when exist more than six authors, list the first six authors followed **by et al.** The **initial** and the **final** pages of the reference should be provided:

Papers published in periodicals:

▪ Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

▪ Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

▪ Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:

▪ Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

THE EDITORS SUGGEST THE AUTHORS TO OBSERVE THE FOLLOWING GUIDELINES WHEN SUBMITTING A MANUSCRIPT:

The **Ideal Manuscript** may not exceed 2500 words.

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

NOTE:

Recent issues of the International Braz J Urol must be observed concerning the presentation form of the manuscript.

INTERNATIONAL
BRAZ J UROL

MANUSCRIPT CHECKLIST

The authors should observe the following checklist before submitting a manuscript to the **International Braz J Urol**

The sequence of manuscript arrangement is according to the Information for Authors.

The Article is restricted to about 2,500 words and 6 authors.

Abbreviations were avoided and are defined when first used and are consistent throughout the text.

Generic names are used for all drugs. Trade names are avoided.

Normal laboratory values are provided in parenthesis when first used.

The references were presented according to the examples provided in the Information for Authors. The references were numbered consecutively, following the sequence that they are mentioned in the text. They were identified in the text using Arabic numeral in parenthesis. The names of all authors were provided. When exist more than six authors, list the first sixauthors followed by et al. The initial and the final pages of the reference should be provided. The number of references must be accordingly to the informed in the Instructions for Authors, depending on the type of manuscript.

The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.

Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.

An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.

A corresponding author with complete address, telephone, Fax, and E-mail are provided.

A submission letter and a disclosure form, signed by all authors, are included.

The authors should included written permission from publishers to reproduce or adapt a previously published illustrations or tables.

Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, is clearly disclosed in the manuscript.

Check that each figure is cited in the text. The illustrations are not merged in the text.

The photographs are supplied as TIFF or JPG files and saved at a resolution of 300 dpi (dots per inch) at final size.

The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not **embed in Word or PowerPoint.**

A list of abbreviations is provided.