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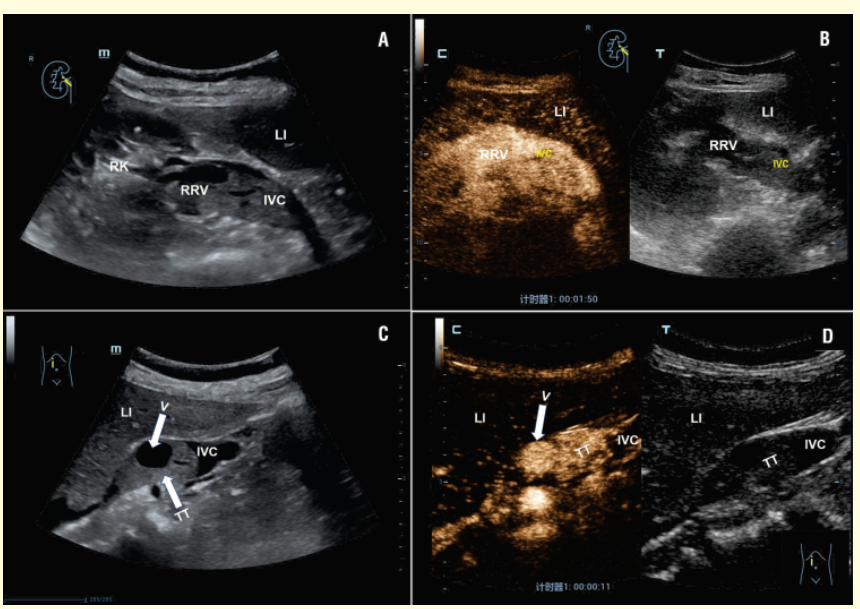

Example case of right-sided renal tumor with a level II IVC thrombus in a 53-year-old female patient. A) B-mode imaging showed solid hypoechoic thrombus in the RRV and IVC. B) CEUS scan showed more lasting, homogeneous, complete marked enhancement of the tumor thrombus in the RRV and IVC. There was adjacent liver washout at 1 min 50s post-injection. C) B-mode imaging showed a formed vessel in the tumor thrombus of the IVC (arrows). D) CEUS scan showed rapid and strong enhancement of the formed vessel in tumor thrombus 11s after injection of microbubbles (*page 98*).

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EDITORIAL
IN THIS ISSUE

Vol. 46 (1): 1-2, January - February, 2020
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A new era of the the *International Brazilian Journal of Urology*

Luciano A. Favorito [1, 2, 3]

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I am a full Professor of Basic Research in Urogenital Research Unit from State University of Rio de Janeiro since 1995 and started to work at the *Int Braz J Urol* in 1999 as a reviewer, invited by Professor Francisco J. B. Sampaio. During this time I have learned a lot from the latest editors and could witness the growth of our journal. Today, the journal is well established and can be considered one of the most respected journals in the urological community.

For the first time, there was a contest for the choice of the editor of the Journal, where the candidates were evaluated by a select examining board composed of five teachers, including the last two editors of the Journal (Drs. Francisco Sampaio and Sidney Glina). With great honor I was chosen as the next editor for the next 4 years with a possibility of renewal.

Currently, the *Int Braz J Urol* is well structured and has an impact of 1,046 on the JCR. Our main goal will be to achieve an increased impact. For this, we have implemented some changes: 1) Only articles submitted in the English language will be accepted; 2) We will end the section of clinical cases, 3) We will be extremely rigorous with the time of review of articles, 4) We will value *ad-hoc* reviewers and greatly increase the level of demand for articles to be accepted, 5) We will create two new sections: a) update in urology, where experts will comment on the main articles published in their sub-specialty in other journals and b) Expert opinion, where experts will make mini reviewes about your area; in this number Dr. Sandro Esteves made a very interesting review about infertiligy (1). With these changes we hope that by the end of our term in 2024 *Int Braz J Urol* will have an impact commensurate with its importance.

This first number of *Int Braz J Urol* under my supervision presents original contributions with a lot of interesting papers in different fields: Prostate Cancer, Renal Stones, Renal Cell Carcinoma, Prostate Biopsy, Urinary Incontinence, Renal Manifestation of Sarcoidosis, Urethral Stricture, Urinary Diversion and Testicular Cancer. The papers came from many different countries such as Brazil, USA, Turkey, China, Spain, Japan, Israel and Qatar, and as usual the editor´s comment highlights some of them. In the present issue we present two important reviews: in page 5 Weintraub and colleagues from Israel (2) reviews in a nice narrative of the epidemiology, diagnosis and pathophysiology of pelvic organ prolapse, and Correia and colleagues from Brazil (3) present in page 15 an important review on renal manifestations of sarcoidosis.

Banno and collegues from Japan (4) present on page 26 an interesting study about computed tomography imaging characteristics of clear cell papillary renal cell carcinoma (CCP), a new subtype of Renal cell carcinoma (RCC) recognized in 2013. The authors studied 12 patients pathologically diagnosed with CCP RCC and concluded that the CT imaging characteristics of CCP RCCs could be categorized into either solid or cystic type.

Dr. Johnston and colleagues from USA (5) performed on page 42 an external validation study about bone scan positivity in non-metastatic, castrate-resistant prostate cancer. The authors performed a retrospective cohort study of 6,509 patients with non-metastatic, castrate-resistant prostate cancer and concluded that previously published risk tables predicted bone scan positivity in men with non--metastatic, castrate-resistant prostate cancer with reasonable accuracy.

Balaban and colleagues from Turkey (6) present on page 60 an interesting study about acute prostatitis after prostate biopsy under ciprofloxacin prophylaxis with or without ornidazole and pre--biopsy enema in 3,479 cases and concluded that repeat biopsy seems to increase the risk of acute prostatitis, while the use of antibiotics effective for anaerobic pathogens seems not to be essential.

Dr. Li and colleagues from China (7) performed on page 92 an amazing study about the role of contrast-enhanced ultrasound (CEUS) in differentiating bland thrombus from tumor thrombus of the inferior vena cava (IVC) in patients with renal cell carcinoma (RCC) in 30 patients who underwent robot-assisted radical nephrectomy with IVC thrombectomy and pathologically confirmed RCC and concluded that CEUS is an effective, inexpensive, and non-invasive method, that could be a reliable tool in the evaluation of IVC thrombus in patients with RCC.

We hope that readers will enjoy the changes made and read and publicize the International Brazilian Journal of Urology.

REFERENCES

1. Esteves SC. Are specialized sperm function tests clinically useful in planning assisted reproductive technology? Int Braz J Urol. 2020;46:116-23.
2. Weintraub AY, Glinter H, Marcus-Braun N. Narrative review of the epidemiology, diagnosis and pathophysiology of pelvic organ prolapse. Int Braz J Urol. 2020;46:5-14.
3. Correia FASC, Marchini GS, Torricelli FC, Danilovic A, Vicentini FC, Srougi M, et al. Renal manifestations of sarcoidosis: from accurate diagnosis to specifi c treatment. Int Braz J Urol. 2020;46:15-25.
4. Banno T, Takagi T, Kondo T, Yoshida K, Iizuka J, Okumi M, et al. Computed tomography imaging characteristics of clear cell papillary renal cell carcinoma. Int Braz J Urol. 2020;46:26-33.
5. Johnston AW, Longo TA, Davis LG, Freedland SJ, Routh JC. Bone scan positivity in non-metastatic, castrate-resistant prostate cancer: external validation study. Int Braz J Urol. 2020;46:42-52.
6. Balaban M, Ozkaptan O, Sevinc C, Boz MY, Horuz R, Kafkasli A, Canguven O. Acute prostatitis after prostate biopsy under ciprofloxacin prophylaxis with or without ornidazole and pre-biopsy enema: analysis of 3.479 prostate biopsy cases. Int Braz J Urol. 2020;46:60-6.
7. Li Q, Wang Z, Ma X, Tang J, Luo Y. Diagnostic accuracy of contrast-enhanced ultrasound for detecting bland thrombus from inferior vena cava tumor thrombus in patients with renal cell carcinoma. Int Braz J Urol. 2020;46:92-100.

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Int Braz J Urol. 2020; 46: 1-2

EDITORIAL

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Best videos of the year for 2019

Philippe E. Spiess [1, 2]

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This year has been another exceptional year for the International Brazilian Journal of Urology with a significant increase of quality video submissions. I am truthfully amazed by the innovative and beautifully depicted videos sent to us from across the world. It is through this commitment to continually refining our surgical approaches and techniques that we will set new benchmarks of excellence in our surgical specialty. In making this selection for best videos of the year, many criteria are taken into account including originality, quality of video depiction and narration, and novelty in re-defining surgical standards. In this regard, I am pleased to announce the top 3 videos of the year. The 1st Prize is awarded to the video by Garisto et al. (1) from the department of urology, Cleveland Clinic (Int Braz J Urol. 2019 Mar 22;45. [Epub ahead of print]) entitled "Robot-assisted repair for ureteroileal anastomosis stricture after cystectomy: technical points" (**see video**). Management of such strictures post-cystectomy can be quite challenging and this highly skilled team from the Cleveland Clinic led by Dr. Kaouk illustrate how it can be approached using a minimally invasive approach in a systematic and methodical manner allowing its reproducibility and adoption by others across the world. The 2nd Prize is awarded to the video by Velilla et al. (2) from the departments of urology, general surgery, and radiology at the Hospital Universitario Marques de Valdecilla in Satander, Spain (Int Braz J Urol. 2019 Mar-Apr;45(2):411). This video entitled "Robotic surgery in the management of complex pelvic endometriosis" (**see video**) highlights how minimally invasive robotic surgery can be offered to patients suffering from multi-organ site endometriosis through the coordination and team work of multi-disciplinary surgical teams. The authors nicely highlight the key steps in conducting such complex procedures offering critical details to conducting such procedures at other international centers of excellence. It is of note that embarking on such multi-organ and specialty procedures requires methodical review of pre-operative imaging and defining the affected sites of disease which will help determine the location/number of port placements, the enumerated steps of the procedure, and which surgical teams should participate and in what specific order they should proceed. This truthfully reminds me of a symphonic orchestra working in a harmonious and coordinated manner. Last but certainly not least, the 3rd prize for best video of the year is awarded to the video by Sonawane et al. (3) from the department of urology at the Muljibhai Patel Urological Hospital in Gujarat, India (Int Braz J Urol. 2019 Jan-Feb;45(1):193). This entitled "Vascular injuries during laparoscopic donor nephrectomy and proposed risk reduction strategies" (**see video**). There are many qualities related to this work including the meticulous review by the authors of their completed cases ultimately providing insight to improving patient outcomes through their only 5 cases (0.6%) of vascular injuries among their large cohort (N=858) of completed

laparoscopic donor nephrectomies between 2011 and 2016. This video very elegantly depicts what can be done to avoid such injuries and if they in fact infrequently occur, how can they be managed to minimize their meaningful sequelae. There are important lessons depicted within this video that broadly apply to many facets of other laparoscopic and open surgical procedures within and outside of urology ie meticulous review of pre-operative imaging and managing such vascular complications through effective and clear communication while maintaining a calm demeanor.

In my concluding remarks, I would like to thank and congratulate our outgoing editor-in-chief Dr Sidney Glina on his exceptional leadership and vision for our journal over his very successful term. Similarly, I would like to congratulate Dr. Luciano A. Favorito in being elected as the new editor-in--chief for our journal and very much look forward to working as part of your executive editorial team.

Warmest regards and best wishes to all our readers and contributors for the holidays and the New Year. Very much looking forward to receiving your quality submissions in 2020.

REFERENCES

1. Garisto J, Bertolo R, Eltemamy M, Campbell R, Kaouk J. Robot-assisted repair for ureteroileal anastomosis stricture after cystectomy: technical points. Int Braz J Urol. 2019 Mar 22;45. [Epub ahead of print].
2. Velilla G, Ballestero R, Gómez M, Zubillaga S, Herrero E, Yllera E, Gutiérrez JL. Robotic surgery in the management of complex pelvic endometriosis. Int Braz J Urol. 2019;45:411.
3. Sonawane P, Ganpule A, Singh A, Sabnis R, Desai MR. Vascular injuries during laparoscopic donor nephrectomy and proposed risk reduction strategies. Int Braz J Urol. 2019;45:193.

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REVIEW ARTICLE

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Narrative review of the epidemiology, diagnosis and pathophysiology of pelvic organ prolapse

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ABSTRACT

The exact prevalence of pelvic organ prolapse is difficult to establish. The anatomical changes do not always consist with the severity or the symptoms associated with prolapse. There are many risk factors associated with pelvic organ prolapse and this review aims to identify the epidemiology and pathophysiology while looking at the known risk factors for pelvic organ prolapse. PubMed search involved a number of terms including: epidemiology, risk factors, reoccurrence indicators, management and evaluation. Several risk factors have been associated with pelvic organ prolapse, all contribute to weakening of the pelvic floor connective tissue/collagen, allowing the pelvic organs to prolapse through the vaginal walls. Among the risk factors are genetic background, childbirth and mode of delivery, previous hysterectomy, menopausal state and the ratio between Estrogen receptors. The "Integral theory" of Petros and the "Levels of Support" model of Delancey enable us to locate the defect, diagnose and treat pelvic organ prolapse.

The currently available demographic data is not reliable enough to properly estimate the true extent of pelvic organ prolapse in the population. However, standardization of the diagnosis and treatment may significantly improve our ability to estimate the true incidence and prevalence of this condition in the coming years.

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INTRODUCTION

Pelvic organ prolapse (POP) is a disturbing problem, which affect many women and their quality of life (1). In the literature, there is a discrepancy regarding the true prevalence of POP which can be related to the type of study performed (2-4). While studies presenting anatomical prolapse observed during gynecological examination describe the prevalence of POP up to 50%, other studies which involve only questionnaires of bothersome symptoms, describe much lower prevalence (2, 3). The actual number of women that undergo intervention for POP seems to be similar to the prevalence described in telephonic surveys (5). Bulge symptoms and other associated prolapse symptoms are more significant than the anatomical changes that can be seen during gynecological examination.

Although many factors were described in association with POP, the relationship between the risk factors themselves is not clear and not always

well understood. Weakness of the endopelvic fascia is the main factor in the etiology of POP and all the known risk factors actually cause weakness and damage of the fascia and therefore may result in herniation of the organs and prolapse (6).

The aim of this narrative review is to describe the actual prevalence of symptomatic POP based on the literature and to try to relate the known risk factors (Figure-1) to the pathophysiology of POP. Understanding the pathophysiology and risk factors, may lead to better diagnosis and treatment.

Methodology

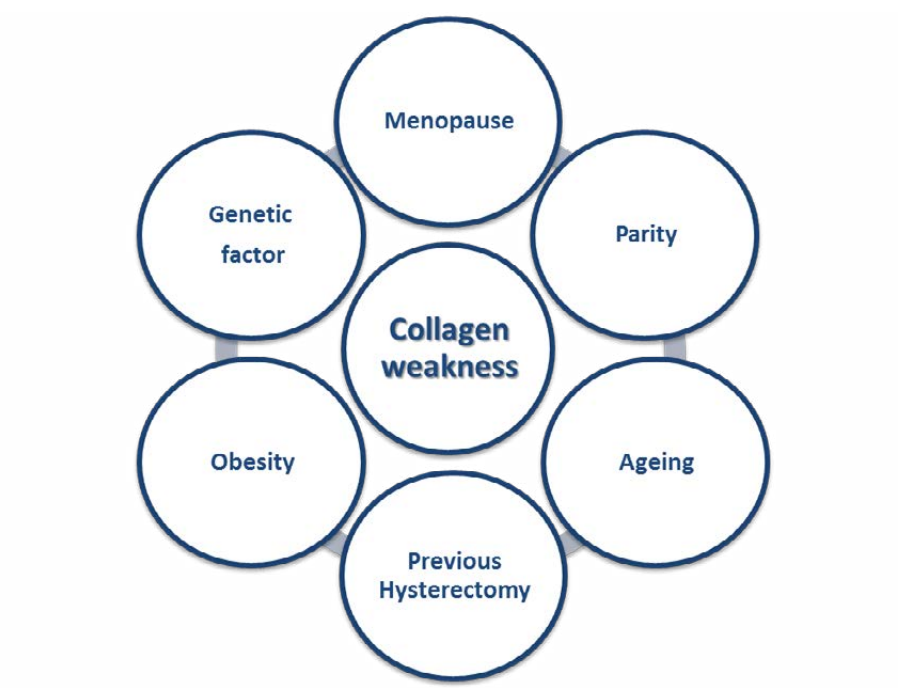
The content of this article was compiled through a literature review of peer reviewed journal articles and studies related to the topic of pelvic organ prolapse (POP). PubMed was the primary database used to search for journal articles and studies for the review. In order to prepare this review we performed a Medline search for English articles using the following key words: "pelvic organ prolapse", "cystocele", "rectocele", "apical prolapse", "epidemiology", "risk factors". We reviewed the article's references as well. We strained to include the most recent articles from the best existing journals for this update of the literature on this topic. A total of 55 references were used to review the epidemiology, pathophysiology, and management of pelvic organ prolapse.

Epidemiology and demographic characteristics of pelvic organ prolapse

Pelvic organ prolapse is defined as a protrusion or herniation of the pelvic organs through the vaginal walls and pelvic floor. It is a common condition that affects many women. However, the exact prevalence is difficult to establish. It is frequently quoted that about 50% of all women will develop POP, but this refers only to the anatomical changes and does not reflect the severity of prolapse or the symptoms associated with prolapse. Therefore, the prevalence of symptomatic POP is actually much lower (1).

The reported prevalence of POP is highly varied according to different studies and is found to be anywhere between 3% and 50% (2-4). These wide variations are due to differences in study design, inclusion criteria, and accompanying indicator symptoms used among studies. For exam-

Figure 1 - Risk factors for pelvic organ prolapse, causing collagen weakness.



ple, studies that are based on telephone surveys without a gynecological examination rely on the subjective bulge sensation reported by women and estimate the prevalence of POP to be between 2.9% and 8.3% (2, 3). In contrast, in other studies that are based on an objective gynecological examination with no regard to women's subjective symptoms, the prevalence of any POP is reported to as high as 50%. There is more than one evaluation method used in order to quantify the extent of any individual prolapse. Grading from 0-4 describes the descent of the prolapse from minimal prolapse to the greatest possible descent. In these studies, most of the women reported POP grade 1 or 2 with the rate of POP grade 3 being only 2%-3% (1, 4). Although, telephonic surveys cannot replace gynecological examination, it seems that they better describe symptomatic POP and are therefore important.

Pelvic organ prolapse can be defined by the descent of the compartment according to the vaginal segment and is divided into anterior, posterior, and apical vaginal compartments. Data regarding the type of prolapse or the compartment most often affected are available from epidemiological studies as well as from studies reporting preoperative evaluation. It has been found that prolapse of the anterior compartment occurs most frequently among the three types and is reported to be twice as prevalent as prolapse of the posterior compartment and three times more prevalent than prolapse of the apical compartment (7, 8). It should be noted that POP is a dynamic condition and that to a certain extent, two thirds of women have a combined prolapse of all three compartments. The prevalence of prolapse of the vaginal cuff following hysterectomy was reported to be as high as 6%-12% (9).

Among women having symptomatic POP, the age distribution increases dramatically. Women between the age of 20-29 account for 6% of the women suffering from POP, while women aged 50-59 years account for 31% with POP and close to 50% of women with POP are aged 80 years or older (10). With increased longevity and an increase in the demographic of women over 65 years, it is expected that in the near future POP will become a major health concern. Wu et al. have estimated that in the USA in 2050, the prevalence of women suffering from symptomatic POP will increase to 46%, which translates to over 5 million individuals (11).

The age association of POP is further revealed by studies identifying those who seek medical consultation and care for their symptoms. The average age of women seeking medical consultation for symptomatic POP is 61 (10). According to the demographic study performed by Luber et al. (12), there is a positive association of increasing age of women and those who seek medical help for POP. The rate of women aged 30-39 who seek medical help for POP is 1.7/1000. The rate increases among women aged 60-69 to 13.2/1000. The highest rate among those seeking medical consult for symptomatic POP was reported in women aged 70-79 and is as high as 18.6/1000 (12).

Other studies that give insight regarding the prevalence of POP are those reporting data on patients who have undergone POP reconstruction surgeries. From these studies it appears that a woman's lifetime risk of undergoing a surgery for POP or stress urinary incontinence (SUI) is 11%-20% (10, 13, 14). However, these data sets do not indicate true prevalence rates of POP for a number of reasons. Many women that suffer from POP may be asymptomatic, or not seek medical attention for other reasons. In addition, many women with POP that seek medical attention are managed conservatively and are not treated with surgery. Lastly, there is inconsistency between studies regarding the grade of POP that requires surgical intervention. Therefore, there is a lack of standardization between the different reports.

As with those who seek medical care and consultation, the prevalence and incidence of POP reconstructive surgery also increases with age (10). By the age of 80 years, the lifetime risk of a woman in the USA undergoing at least one surgery for POP is 6.3% and the risk of recurrent surgery is 30% (13). In Australia, a woman's risk of undergoing at least one surgery for POP is threefold higher at 19% (14). This difference may be explained in part by differences in surgical practice, incorporation of new surgical techniques, medical

insurance coverage, and different cultural perceptions of quality of life (QoL). The annual rate of POP surgery in the USA is 1.5-1.8/1000 women with the highest rates reported among women aged 60-69 years. This is comparable to the rate of women referring to medical help due to POP (5).

Another important epidemiological indicator is the rate of recurrent POP and the need for recurrent surgery. This data is unreliable and the prevalence is not completely clear because not every recurrence is symptomatic. In addition, the evaluation of POP that determines the need for repeat surgery has changed in recent years. While in the past prolapse recurrence was considered a surgical failure, in recent years, symptom relief and improved QoL are recognized as the determining factors for surgical success. There is approximately a 30% recurrent prolapse rate following POP repair surgery (13). However, this approximation does not take into account the stage of prolapse or presence of symptoms. Recently, the two main international organizations in urogynecology, the International Continence Society (ICS) and the International Urogynecological Association (IUGA) have presented a joint report on the terminology for reporting outcomes of surgical procedures for POP that incorporates anatomical outcomes as well as subjective patient's symptoms, QoL and satisfaction (15).

Risk factors and Pathophysiology of POP

Several risk factors have been associated with POP. All risk factors contribute to weakening of the pelvic floor connective tissue/collagen, causing the pelvic organs to prolapse through the vaginal walls and pelvic floor (Figure-1). There are predisposing, non-modifiable factors including race, gender and genetic make-up. Other promoting risk factors for which intervention or prevention can be of benefit, include occupation, obesity, smoking, and infection, and there are inciting risk factors such as childbirth causing muscle, connective tissue, vascular and neural damage (16).

a) BMI/Obesity

Obesity directly affects symptoms of pelvic organ prolapse. A chronic increase in intra-abdominal pressure, nerve damage and co-morbidities of obese individuals all contribute to pelvic floor dysfunction (17, 18). Intra-abdominal pressure causes excessive strain on pelvic structures, including the pudendal nerve. Co-morbidities such as diabetes contribute to poor tissue features through neuropathy and genetic background and joint hypermobility.

b) Genetic

It is well established that there is a genetic predisposition for POP, independent of all other risk factors that may impact or aggravate the condition. In women with a family history of prolapse there is a 2.5-fold increased incidence of POP compared with the general population (19). Many women with POP report having relatives with POP, urinary incontinence and/or an abdominal or inguinal hernia (20). In addition, younger women with POP have a higher incidence of POP among first-degree relatives than those who develop POP at an older age (21).

The association between POP and other conditions with impaired collagen quality has been shown in many studies, which further implies a genetic predisposition. The incidence of collagen diseases such as varicose veins and joint hypermobility was increased in women with POP and in a recent meta-analysis of 39 studies, joint hypermobility as an indicator for POP was determined to be clinically relevant (22).

The strength of collagen, the main component of the body's connective tissue, and specifically of the pelvic floor fascia and ligaments, is determined by genetic factors. The type of collagen and the body's ability to replace damaged collagen with collagen that is strong and of high quality is also determined by genetic factors (23).

Several studies have attempted to identify and characterize the genes that are responsible for POP. In a recent meta-analysis it was found that collagen type 3 alpha 1 (COL3A1) rs1800255 genotype AA was significantly associated with POP in an Asian and Dutch population compared with a reference genotype population (OR 4.79; 95% CI 1.91-11.98; P <0.001) (24). Other studies investigated different populations; however, they were

limited by a small sample size, preventing them from drawing meaningful conclusions. With the advances seen in molecular biology and the possibility to decipher entire genes it is conceivable that in the near future scientists will find the genes responsible for collagen strength and therefore those that predispose POP.

a) Obstetrical and gynecological history

Parity: Multi-parity may be the strongest predisposing factor to POP. Women with one child show a fourfold increased likelihood to experience POP requiring hospital attention and those with two children an 8.4 times greater likelihood, compared with nulliparous women (25). Interestingly, while parity is an established risk factor for primary POP, it is not a risk factor for recurrence (26).

Mode of delivery and obstetrical trauma: Vaginal delivery has an extensive role in pelvic floor damage and the eventual development of POP. It is understood that most of the damage to the pelvic floor occurs during first and second deliveries (27). Pelvic floor imaging studies have demonstrated the "Ballooning" phenomenon after delivery. This phenomenon describes the widening of the pelvis during the Valsalva maneuver that represents the expansion of the levator-ani muscles. This phenomenon can be demonstrated after delivery using a 3D ultrasound and in a vaginal examination (28).

Although rare, POP in women with no vaginal deliveries is possible. Cesarean section serves as a protective factor from POP if there was no additional vaginal delivery (29). Instrumental deliveries increase the risk for POP, forceps delivery in particular (30).

As an added obstetrical risk factor, cervical elongation is also reported to affect approximately 40% of women with uterine prolapse. The cervical length in women with uterine prolapse was measured to be about 36% longer than in women without uterine prolapse (31).

Hysterectomy: An increased risk for central compartment prolapse is noted in women who have undergone hysterectomy as compared with women with in situ uterus. Possible explanations for this observation include: intraoperative damage to the pelvic connective tissue, injury to the pelvic blood supply and innervation, as well as not enough emphasis placed on the secure fixation or suspension of the vaginal apex in many hysterectomy procedures. According to a cohort study that evaluated 160.000 women following hysterectomy, the risk of developing POP was 3.2% compared with only 2% in controls (32). Compared with non-hysterectomized controls, the overall Hazard ratios (HR) for prolapse surgery was 1.7 (95% CI, 1.6 to 1.7) with the highest risks observed in women having had a vaginal hysterectomy (HR 3.8; 95% CI, 3.1 to 4.8). However, it should be noted that the indication and type of hysterectomy were not reported. It is therefore unclear what is the exact proportion of women who have undergone a vaginal hysterectomy due to previous POP. According to other studies it is clarified that the risk of developing an apical prolapse following a vaginal hysterectomy due to POP is five-fold higher even if a prolapse correction was performed in the primary surgery (33).

a) Menopause

While advanced age is a risk factor for POP as discussed in earlier sections, and menopause is a consequence of age, there is a straight association between menopause and an increased risk for POP that is independent of age or parity (34, 35). The hormonal changes in menopause cause a drop in the systemic estrogen concentrations, and a hypoestrogenic environment in the pelvic organs contributes to alterations in the composition and strength of collagen (36).

Studies that evaluated the influence of estrogen and of selective estrogen receptor modulators (SERM) on the development of POP have shown conflicting results. According to some studies, Raloxifene and Tamoxifen have worsened the severity of POP as compared with estrogen and placebo (37, 38). In contrast, a prospective study that investigated the impact of Raloxifene treatment on the development of POP showed a 50% decrease in surgical intervention for POP in a group of post-menopausal women (39). An increase in the rate of POP was demonstrated with the use of other drugs of the SERM family such as

Levormeloxifene and Idoxifene and POP has even been stated as a side effect of these medications (40, 41).

The impact of estrogen on the tissue is not only dependent on the estrogen concentrations but also on the expression of estrogen receptors. Estrogen and estrogen receptors modify genes that encode growth factors in the extracellular matrix. During menopause, changes in the concentration and quality of collagen, connective tissue morphology and the role of estrogen in the metabolism of collagen are all indicators of the involvement of estrogen in the development of POP (36). The concentration of collagen in the vagina is determined by the equilibrium between collagen metabolism and catabolism. Estrogen receptors can be found among other tissues, in the nucleus of connective tissue cells, smooth muscle cells in the bladder trigone, in the vaginal mucosa, in the levator-ani muscle and in the utero-sacral ligaments, of which the utero-sacral and the cardinal ligaments are essential components of organ support (42). In post-menopausal women with POP, significantly lower concentrations of serum estrogen and lower concentrations of estrogen receptors in the pelvic floor ligaments were found as compared to women without POP (43, 44).

The type of estrogen receptors is also a factor associated with the development of POP. In women with POP an alteration in the ratio of alpha and beta estrogen receptors was noted. In post-menopausal women with POP a 1.5-2.5 fold decrease in alpha estrogen receptors was found. Moreover, in pre-menopausal women without POP, an increase in beta estrogen receptors was measured as compared to women with POP (45).

The apparent influence of estrogen and SERM on the synthesis of estrogen receptors may explain the contradicting association between SERM and the incidence of POP, most likely by altering the ratio between alpha and beta estrogen receptors. Much more research is needed in order to fully understand these associations.

In conclusion, conditions that cause an increase in intra-abdominal pressure such as chronic cough and constipation, obesity, modifiable risk factors such as a lifestyle or occupations that require lifting heavy loads and medical conditions that involve the connective tissue such as Ehlers--Danlos syndrome or Marfan syndrome are considered risk factors for POP (46-48).

While individual risk factors affecting the prevalence of POP such as age, vaginal deliveries and race are well identified, comorbidities such as DM together with hypertension must be considered in the development of the condition (49).

Identification and Management of POP

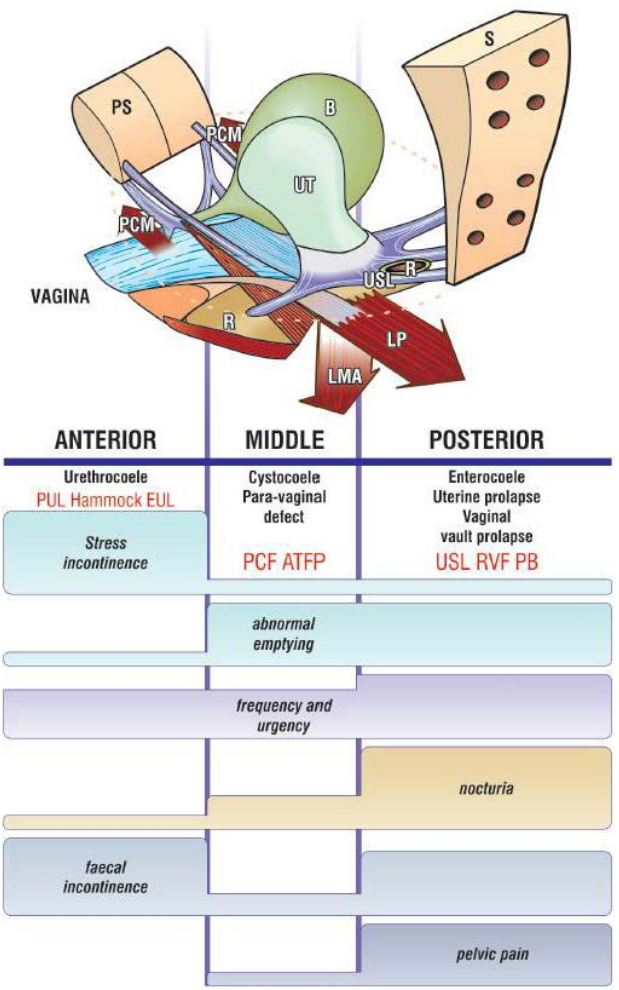
The current understanding of the pelvic floor is based on the work of two modern anatomists: Peter Petros and John Delancey. These two researchers have studied the pelvic floor extensively and have incorporated in their studies advanced dynamic imaging techniques.

The "Integral Theory"

The "Integral Theory" represents the foundation of our current knowledge of the development of POP. Published by Peter Petros in 1990, it is the cornerstone of our understanding of the pathogenesis of prolapse as well as the definition of the treatment (6). According to this theory, POP and its related symptoms result from over-laxity of the vaginal connective tissue or its supporting ligaments. The integral theory includes four components: normal function, dysfunction, diagnosis, and treatment (50).

The bladder, vagina, and rectum are pelvic organs held in place by supporting ligaments including the pubo-urethral (PUL) and pubo vesical (PVL) ligaments, the utero-sacral ligaments (USL), the cardinal ligaments, and the arcus tendineus fascia pelvis (ATFP) (Figure-2). The pelvic floor fascia joins these ligaments and the perineal body. The main component of the pelvic floor fascia and of the ligaments is collagen. The pelvic floor muscles pull back the pelvic organs and the pelvic floor fascia in three different directions providing them with support and maintaining their form and strength (Figure-1). The pelvic floor ligaments and fascia can be depicted as a suspension bridge, where the strength of the bridge is dependent on the strength of the ligaments. Injury or damage to one of the ligaments will bring about the collapse of the bridge. Likewise, injury or weakening of one of the

Figure 2* - Schematic diagram of the pelvis organs, ligaments, muscles and the connection between them according to the integral theory of Peter Petros.



*source www.intergraltheory.com, Petros with permission

PUL = Pubourethral ligament; **PCF =** Pubocervocal fascia; **ATFP =** Arcus tendineus fascia pelvis; **CL =** Cardinal ligament/cervical ring; **USL =** Uterosacral ligament; **RVF =** Rectovaginal fascia; **PB =** Perineal body

pelvic floor ligaments will cause a herniation of the pelvic organs according to the location of the affected ligament. According to the integral theory the pelvis is divided into three areas: anterior, middle, and posterior, in which connective tissue laxity affects the organs and their function (Figure-1). It should be noted that while there may be severe symptoms of prolapse, this may not correlate with the actual severity of prolapse and may occur with minimal prolapse (51, 52).

According to the integral theory a discreet examination is performed by area of the pelvic floor in order to evaluate the damage and to focus the treatment to a specific area (50). Moreover, it helps us to understand the symptoms and the location of the prolapse as well as to understand that the main injury to the pelvic floor is in the pelvic floor connective tissue, namely, the pelvic floor fascia and the ligaments.

The "Levels of Support" model

John Delancey has described the levels of support model, according to which support to the pelvic organs is divided into three levels (53, 54). Delancey, like Petros, acknowledges that the connective tissues, the pelvic floor fascia and the pelvic floor ligaments, are responsible for holding the pelvic organs in place and that injury to each level of support causes damage to a specific area. Additionally, Delancey's model enables the diagnosis and treatment of the prolapse by level of injury. Delancey has used advanced imaging technologies to predict prolapse. Specifically, using magnetic resonance imaging (MRI), he studied the dynamics of the supporting ligaments at rest and during the Valsalva maneuver, and the respective change in prolapse (55).

Petros and Delancey's work enable us to locate, diagnose and treat POP but do not provide answers regarding the causes for weakening of the connective tissue and pelvic floor ligaments. It is still not entirely understood why some multiparous women do not report prolapse symptoms and may have no or only minimal POP, while others will suffer symptomatic prolapse at a young age after only one delivery. The answers regarding the causes of pelvic floor connective tissue weakening and development of vaginal herniation may be derived from a closer look at prolapse risk factors.

Summary

From a public health point of view, POP has a tremendous economic burden on health systems. The increase in life expectancy and the movement towards improved QoL, contribute not only to the increase in the prevalence of POP but also to the increase in prevalence of women seeking treatment and solutions for their symptoms.

The currently available demographic data is not reliable enough to properly estimate the true extent of POP in the population. However, a continuing joint effort of the international associations (IUGA and ICS) in standardization of the diagnosis and treatment of POP, may significantly improve our ability to estimate the true incidence and prevalence of this condition in the coming years.

The understanding that the pelvic floor relies on the pelvic floor fascia and ligaments for its support enables us to identify the specific injury causing the prolapse and to treat it accordingly. We owe this understanding to the works of Peter Petros and John Delancy. However, the causes for weakening of the connective tissue and pelvic floor ligaments is still unclear and answers may be found while looking closer at the risk factors. It is evident that there is a strong genetic basis for POP. Identifying the genes responsible for the quality of collagen will enable us to council high risk nulliparous women regarding possible preventive measures including physiotherapy, avoidance of strenuous activity and even elective cesarean delivery. A hypoestrogenic environment especially in post-menopausal women has a significant role in the development of POP. This is illustrated by medications from the SERM family impacting the development or prevention of POP. Continuing research and bettering our understanding of the role of estrogen receptors and the change in ratio between the types of these receptors may lead to the development of new drugs to reinforce damaged collagen, prevent, or even reverse POP.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Barber MD, Maher C. Epidemiology and outcome assessment of pelvic organ prolapse. Int Urogynecol J. 2013;24:1783-90.
2. Tegerstedt G, Maehle-Schmidt M, Nyrén O, Hammarström M. Prevalence of symptomatic pelvic organ prolapse in a Swedish population. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16:497-503.
3. Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, et al. Pelvic Floor Disorders Network. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008;300:1311-6.
4. Swift SE, Tate SB, Nicholas J. Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse? Am J Obstet Gynecol. 2003;189:372-7.
5. Shah AD, Kohli N, Rajan SS, Hoyte L. The age distribution, rates, and types of surgery for pelvic organ prolapse in the USA. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19:421-8.
6. Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynecol Scand Suppl. 1990;153:7-31.
7. Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol. 2002;186:1160-6.
8. Summers A, Winkel LA, Hussain HK, DeLancey JO. The relationship between anterior and apical compartment support. Am J Obstet Gynecol. 2006;194:1438-43.
9. Aigmueller T, Dungl A, Hinterholzer S, Geiss I, Riss P. An estimation of the frequency of surgery for posthysterectomy vault prolapse. Int Urogynecol J. 2010;21:299-302.
10. Wu JM, Vaughan CP, Goode PS, Redden DT, Burgio KL, Richter HE, et al. Prevalence and trends of symptomatic pelvic floor disorders in U.S. women. Obstet Gynecol. 2014;123:141-8.
11. Wu JM, Hundley AF, Fulton RG, Myers ER. Forecasting the prevalence of pelvic floor disorders in U.S. Women: 2010 to 2050. Obstet Gynecol. 2009;114:1278-83.
12. Luber KM, Boero S, Choe JY. The demographics of pelvic floor disorders: current observations and future projections. Am J Obstet Gynecol. 2001;184:1496-501.
13. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89:501-6.
14. Smith FJ, Holman CD, Moorin RE, Tsokos N. Lifetime risk of undergoing surgery for pelvic organ prolapse. Obstet Gynecol. 2010;116:1096-100.
15. Toozs-Hobson P, Freeman R, Barber M, Maher C, Haylen B, Athanasiou S, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for reporting outcomes of surgical procedures for pelvic organ prolapse. Int Urogynecol J. 2012;23:527-35.
16. Hallock JL, Handa VL. The Epidemiology of Pelvic Floor Disorders and Childbirth: An Update. Obstet Gynecol Clin North Am. 2016;43:1-13.

17. Ramalingam K, Monga A. Obesity and pelvic floor dysfunction. Best Pract Res Clin Obstet Gynaecol. 2015;29:541-7.
18. de Sam Lazaro S, Nardos R, Caughey AB. Obesity and Pelvic Floor Dysfunction: Battling the Bulge. Obstet Gynecol Surv. 2016;71:114-25.
19. Lince SL, van Kempen LC, Vierhout ME, Kluivers KB. A systematic review of clinical studies on hereditary factors in pelvic organ prolapse. Int Urogynecol J. 2012;23:1327-36.
20. Segev Y, Auslender R, Feiner B, Lissak A, Lavie O, Abramov Y. Are women with pelvic organ prolapse at a higher risk of developing hernias? Int Urogynecol J Pelvic Floor Dysfunct. 2009;20:1451-3.
21. Alcalay M, Stav K, Eisenberg VH. Family history associated with pelvic organ prolapse in young women. Int Urogynecol J. 2015;26:1773-6.
22. Veit-Rubin N, Cartwright R, Singh AU, Digesu GA, Fernando R, Khullar V. Association between joint hypermobility and pelvic organ prolapse in women: a systematic review and meta-analysis. Int Urogynecol J. 2016;27:1469-78.
23. Reid RI, You H, Luo K. Site-specific prolapse surgery. I. Reliability and durability of native tissue paravaginal repair. Int Urogynecol J. 2011;22:591-9.
24. Ward RM, Velez Edwards DR, Edwards T, Giri A, Jerome RN, Wu JM. Genetic epidemiology of pelvic organ prolapse: a systematic review. Am J Obstet Gynecol. 2014;211:326-35.
25. Patel DA, Xu X, Thomason AD, Ransom SB, Ivy JS, DeLancey JO. Childbirth and pelvic floor dysfunction: an epidemiologic approach to the assessment of prevention opportunities at delivery. Am J Obstet Gynecol. 2006;195:23-8.
26. Vergeldt TF, Weemhoff M, IntHout J, Kluivers KB. Risk factors for pelvic organ prolapse and its recurrence: a systematic review. Int Urogynecol J. 2015;26:1559-73.
27. Sze EH, Sherard GB 3rd, Dolezal JM. Pregnancy, labor, delivery, and pelvic organ prolapse. Obstet Gynecol. 2002;100(5 Pt 1):981-6.
28. Khunda A, Shek KL, Dietz HP. Can ballooning of the levator hiatus be determined clinically? Am J Obstet Gynecol. 2012;206:246.e1-4.
29. Leijonhufvud A, Lundholm C, Cnattingius S, Granath F, Andolf E, Altman D. Risks of stress urinary incontinence and pelvic organ prolapse surgery in relation to mode of childbirth. Am J Obstet Gynecol. 2011;204:70.
30. Handa VL, Blomquist JL, McDermott KC, Friedman S, Muñoz A. Pelvic floor disorders after vaginal birth: effect of episiotomy, perineal laceration, and operative birth. Obstet Gynecol. 2012;119(2 Pt 1):233-9.
31. Berger MB, Ramanah R, Guire KE, DeLancey JO. Is cervical elongation associated with pelvic organ prolapse? Int Urogynecol J. 2012;23:1095-103.
32. Altman D, Falconer C, Cnattingius S, Granath F. Pelvic organ prolapse surgery following hysterectomy on benign indications. Am J Obstet Gynecol. 2008;198:572.e1-6.
33. Blandon RE, Bharucha AE, Melton LJ 3rd, Schleck CD, Babalola EO, Zinsmeister AR, et al. Incidence of pelvic floor repair after hysterectomy: A population-based cohort study. Am J Obstet Gynecol. 2007;197:664.
34. Tinelli A, Malvasi A, Rahimi S, Negro R, Vergara D, Martignago R, et al. Age-related pelvic floor modifications and prolapse risk factors in postmenopausal women. Menopause. 2010;17:204-12.
35. Sze EH, Hobbs G. A prospective cohort study of pelvic support changes among nulliparous, multiparous, and pre- and post-menopausal women. Eur J Obstet Gynecol Reprod Biol. 2012;160:232-5.
36. Jackson SR, Avery NC, Tarlton JF, Eckford SD, Abrams P, Bailey AJ. Changes in metabolism of collagen in genitourinary prolapse. Lancet. 1996;347:1658-61.
37. Vardy MD, Lindsay R, Scotti RJ, Mikhail M, Richart RM, Nieves J, et al. Short-term urogenital effects of raloxifene, tamoxifen, and estrogen. Am J Obstet Gynecol. 2003;189:81-8.
38. Albertazzi P, Sharma S. Urogenital effects of selective estrogen receptor modulators: a systematic review. Climacteric. 2005;8:214-20.
39. Goldstein SR, Neven P, Zhou L, Taylor YL, Ciaccia AV, Plouffe L. Raloxifene effect on frequency of surgery for pelvic floor relaxation. Obstet Gynecol. 2001;98:91-6.
40. Hendrix SL, McNeeley SG. Effect of selective estrogen receptor modulators on reproductive tissues other than endometrium. Ann N Y Acad Sci. 2001;949:243-50.
41. Goldstein SR, Nanavati N. Adverse events that are associated with the selective estrogen receptor modulator levormeloxifene in an aborted phase III osteoporosis treatment study. Am J Obstet Gynecol. 2002;187:521-7.
42. Rechberger T, Donica H, Baranowski W, Jakowicki J. Female urinary stress incontinence in terms of connective tissue biochemistry. Eur J Obstet Gynecol Reprod Biol. 1993;49:187-91.
43. Lang JH, Zhu L, Sun ZJ, Chen J. Estrogen levels and estrogen receptors in patients with stress urinary incontinence and pelvic organ prolapse. Int J Gynaecol Obstet. 2003;80:35-9.
44. Ewies AA, Thompson J, Al-Azzawi F. Changes in gonadal steroid receptors in the ardinal ligaments of prolapsed uteri: immunohistomorphometric data. Hum Reprod. 2004;19:1622-8.

45. Zbucka-Kretowska M, Marcus-Braun N, Eboue C, Abeguile G, Wolczynski S, Kottler ML, et al. Expression of estrogen receptors in the pelvic floor of pre- and post-menopausal women presenting pelvic organ prolapse. Folia Histochem Cytobiol. 2011;49:521-7.
46. Spence-Jones C, Kamm MA, Henry MM, Hudson CN. Bowel dysfunction: a pathogenic factor in uterovaginal prolapse and urinary stress incontinence. Br J Obstet Gynaecol. 1994;101:147-52.
47. Jørgensen S, Hein HO, Gyntelberg F. Heavy lifting at work and risk of genital prolapse and herniated lumbar disc in assistant nurses. Occup Med (Lond). 1994;44:47-9.
48. Carley ME, Schaffer J. Urinary incontinence and pelvic organ prolapse in women with Marfan or Ehlers Danlos syndrome. Am J Obstet Gynecol. 2000;182:1021-3.
49. Isık H, Aynıoglu O, Sahbaz A, Selimoglu R, Timur H, Harma M. Are hypertension and diabetes mellitus risk factors for pelvic organ prolapse? Eur J Obstet Gynecol Reprod Biol. 2016;197:59-62.
50. Petros PE, Woodman PJ. The Integral Theory of continence. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19:35-40.
51. Petros P. The integral system. Cent European J Urol. 2011;64:11019.
52. Petros PE. New ambulatory surgical methods using an anatomical classification of urinary dysfunction improve stress, urge and abnormal emptying. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8:270-7.
53. DeLancey JO. Anatomy and biomechanics of genital prolapse. Clin Obstet Gynecol. 1993;36:897-909.
54. DeLancey JO. The anatomy of the pelvic floor. Curr Opin Obstet Gynecol. 1994;6:313-16.
55. Luo J, Betschart C, Chen L, Ashton-Miller JA, DeLancey JO. Using stress MRI to analyze the 3D changes in apical ligament geometry from rest to maximal Valsalva: pilot study. Int Urogynecol J. 2014;25:197-203.

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REVIEW ARTICLE

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Renal manifestations of sarcoidosis: from accurate diagnosis to specific treatment

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disease characterized by epithelioid non-caseating granulomas associated with clinical and radiologic findings. The cause of this disease is still uncertain. Sarcoidosis affects mostly lungs and lymph nodes and is not usually considered a urological disease, therefore, this etiology may be overlooked in several urological disorders, such as hypercalcemia, hypercalciuria and nephrolithiasis. It affects all races and genders. This review aims to describe the urological manifestations of sarcoidosis and to elucidate how the disease may affect the management of numerous urological conditions.

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INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease characterized by non-caseating epithelioid granulomas in association with clinical and radiologic findings. The cause of this disease is still uncertain. Recent findings suggest that sarcoidosis is related to a chronic immune response caused by exposure to common environmental factors such as Propionibacterium or airborne organic or inorganic material (1), most probably a sum of several immune system and environmental factors (2). It affects all races and genders; however, women are 30% more likely to be affected than men and African-Americans (36/100.000) are more commonly affected than Caucasians (11/100.000) (3). In Europe the incidence is higher in northern countries, 20-40/100.000 at general, up to 121/100.00 in Sweden and lower in southern countries like England (5/100.000) and Spain (1.36/100.000) (4). Japan has a reported pre-

valence of 0.3-1.7/100.000 (5). Brazil does not have recent prevalence studies; the only one was published in 1985 with an estimative of 10 cases per 100.000 inhabitants (4). Genetic propensity may explain the heterogeneity at appearance and the severity of the cases in different ethnic groups and races (2).

Patients with sarcoidosis usually presents with symptoms before the age of 50, with a peak between 20-39 years old. Suggestive findings on chest x-ray of asymptomatic patients are also another form of diagnosis. However, cough, shortness of breath, fatigue or night sweats may be present (6). Most patients with sarcoidosis present one of the following: intrathoracic lymphadenopathy, pulmonary involvement, cutaneous symptoms or eye impairment. Skin manifestations include macules, papules, simple or multiple plaques, which can commonly affect the face, posterior neck, torso and extremities. Erythema nodosum may be present transitorily in 10% of the patients, most commonly in women (7). Most patients with sarcoidosis will experience remission of the disease and will never require specific treatment. However, a third will experience chronic potentially severe disease and ultimately the specific mortality rate may be up to 5% (1). Treatment is mainly based on corticosteroids or immunosuppressive agents to control symptoms.

Sarcoidosis is not usually considered a urological disease, affecting mostly lungs and lymph nodes. For that reason, it may be overlooked when it affects the urinary tract. However, urinary impairment of the disease is not rare and may lead to conditions treated by the urologist such as nephrolithiasis. Moreover, the disease may also produce clinical manifestations that can mimic severe urological disorders such as testicular nodules, renal masses, or even PET positive lymphadenopathy, leading to misinterpretations of early stage urological malignancies (6). The aim of this study is to review how sarcoidosis may affect and interact with several urological illnesses and to describe how to perform an accurate diagnosis and a patient-centered approach.

MATERIALS AND METHODS

An online review was done searching for urological conditions and manifestations associated with sarcoidosis. A research was performed using the key words “sarcoidosis” combined with the urological terms “calculus”, “calculi”, “nephrolithiasis”, “hypercalciuria”, “kidney”, “renal” and “urinary” published until June 2017 in PubMed and Google Scholar database. The results of more than 1.000 articles were summed up to 80 articles and all the relevant information was gathered, organized, and brought to discussion, in addition, the significant references quoted in the selected articles where added to the research.

Two separate urologists performed the online search and reviewed all papers considered suitable and relevant for this analysis. Because of the paucity of high-quality publications, not only prospective and review papers but also case control and case series studies were included in the final analysis. After extensive evaluation and analysis of the data, the information regarding urological manifestations of Sarcoidosis was divided in specific sessions to facilitate and summarize the findings: hypercalcemia and hypercalciuria; nephrolithiasis and nephrocalcinosis, granulomatous interstitial nephritis, glomerular disease and tubular dysfunction, diagnosis and treatment.

RESULTS

Sarcoidosis has a wide range of renal manifestations, most of them related to calcium metabolism, which may ultimately cause renal dysfunction. The focus of our review is the urological manifestations of the disease that may also coexist.

Hypercalcemia and Hypercalciuria

The calcium metabolism disorders occur in patients with sarcoidosis and are presented by hypercalcemia or hypercalciuria due to activated macrophages expressing 1alpha-hydroxilase in sarcoid granulomas (8), this leads to increased levels of 1.25 dihydroxy vitamin D (calcitriol), resulting in high calcium absorption from the bowels (9). Hypercalcemia is present in 10 to 17% of patients with sarcoidosis (10). An altered level of vitamin D and hypercalcemia causes a suppression of parathyroid hormone (10). The suppressed PTH and this overloaded blood calcium is urine excreted, causing hypercalciuria - 24-hour urina-

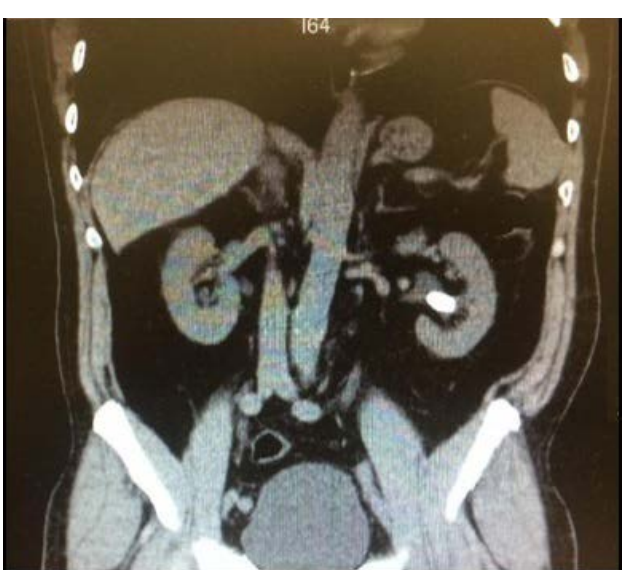
ry levels of calcium above 300mg/dL. Hypercalciuria may be found in 2-5% in healthy adults and up to 62% (11) in patients with sarcoidosis, and a more severe state occurs in 10-20% (6). Excessive sunlight or vitamin D ingestion may worsen the case. These parameters may change according to disease activity or a patient's total ultra-violet light exposure (12). Hypercalciuria predisposes to nephrolithiasis and obstructive uropathy (13).

Hypercalcemia is responsible for a decrease in glomerular filtration rate by vasoconstriction of the afferent arteriole. Also, it inhibits sodium-potassium ATPase leading to urinary sodium wasting with polyuria and dehydration. Finally, a reduced sensitivity to anti-diuretic hormone impairs urinary concentration. Acute tubular necrosis may occur due to intracellular calcium overload and tubular obstruction by calcium precipitates. Hypercalciuria ultimately leads to nephrolithiasis. In the acute phase, the consequences of hypercalcemia and hypercalciuria are reversible but once fibrosis takes place, the damage becomes irreversible (12, 14).

Nephrolithiasis and Nephrocalcinosis

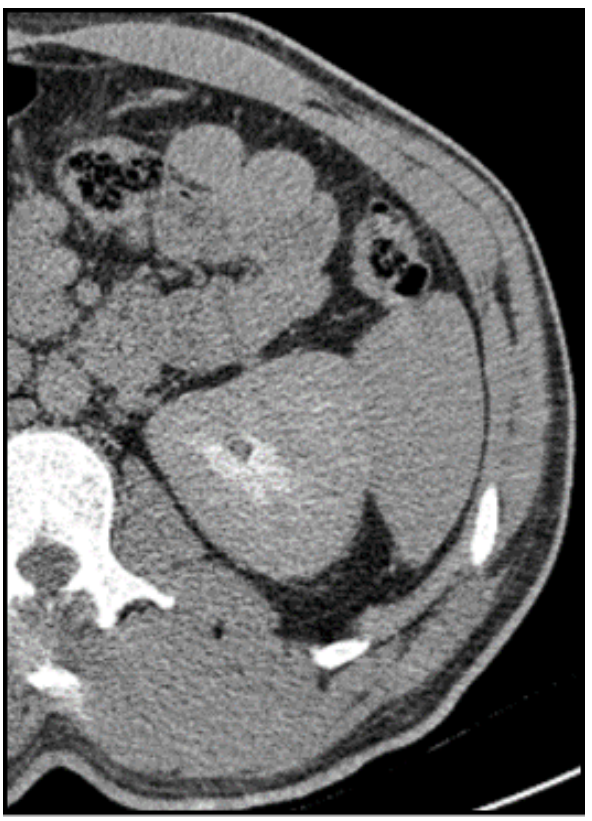
Nephrolithiasis (Figure-1) has been found in about 10% of patients with sarcoidosis, with a prevalence range of 3% to 14%, (14) and hypercalciuria may not be present in all cases at the moment of the diagnosis or when the calculus becomes symptomatic (9). Nephrolithiasis has been referred as the first sign for the diagnosis of sarcoidosis in some patients (11-17). In studies with a careful review of patient's medical history, renal colic was the first sign of the disease in 2.2% of cases (10). However, the diagnosis was done in only half of the patients by the time of the renal calculi diagnosis. The other half of patients had their diagnosis only when other symptoms of chronic sarcoidosis became clinically significant. In these studies, most patients with nephrolithiasis had pulmonary involvement on chest x-ray and the majority also had palpable lymphadenopathy or cutaneous lesions. This combination of findings should alarm the urologist and patients presenting with calcium-based kidney stones that otherwise would be in a low-risk group for nephrolithiasis, such as African American females, who should undergo a lymphadenopathy and skin physical examination and chest x-ray for signs of sarcoidosis.

Figure 1 – Nephrolitiasis.



Nephrocalcinosis (Figure-2) is a rare impairment and is a result of chronic hypercalciuria (16, 17). It is present in less than 5% of patients with sarcoidosis but in a higher rate of patients with renal insufficiency (9). It is a condition related to the calcification of the renal parenchyma and tubules frequently associated with sarcoidosis among other disorders. Advanced macroscopic disease often diagnosed by imaging studies in individuals suspected to have clinical and laboratory findings of sarcoidosis, however, usually is an incidental finding in asymptomatic patients with otherwise unremarkable laboratory parameters. The diagnosis of the initial stages of nephrocalcinosis can be exposed through renal biopsy demonstrating calcium deposits of either calcium phosphate or calcium oxalate on analysis (18). Ultrasound (US) and Computed Tomography (CT) are the preferred diagnostic modalities for nephrocalcinosis as they have sensitivity values of 85 to 90% and 81 to 86%, respectively, with more specificity for the CT - 83% to 89% then the US - 66% to 71% (19). Renal studies with biopsy demonstrated renal sarcoid infiltration in 7-40%, most likely the epithelioid granuloma (11), and it was found up to 20% patients affected in post-mortem dissection (20). These cases might present with sterile leukocyturia, hematuria and proteinuria. In present times, renal granulomas

Figure 2 – Nephrocalcinosis.



are rare thought when present may simulate kidney neoplasia (2).

Granulomatous interstitial nephritis

It is the most common renal lesion seen on biopsy. The true incidence of granulomatous interstitial nephritis is unknown. In autopsy studies, granulomatous infiltrate in kidney tissue was found in up to 23% and in small case series of renal biopsy the incidence of granulomatous interstitial nephritis was 48%, most of them clinically silent (13).

The urinary manifestations of interstitial nephritis are like those of other tubule-interstitial diseases. Urinalysis findings will be most commonly normal, however, these may show sterile pyuria, microscopic hematuria, glycosuria, and hypercalciuria (21, 22).

Glomerular disease and tubular dysfunction

A variety of lesions including membranous nephropathy, focal segmental sclerosis, mesangioproliferative glomerulonephritis, IgA nephropathy and crescent glomerulonephritis are described as glomerular involvement, indistinguishable from the primary form. Tubular dysfunctions can be present in isolated proximal or distal renal tubular acidosis or Fanconi's syndrome. Polyuria is the usual clinical feature, mostly because of hypercalcemia disorders (18).

Diagnosis

Sarcoidosis is a diagnosis of exclusion; almost half of the patients takes more than 3 physician visits until the diagnosis is made (23). But up to 90% of the times an altered x-ray of the chest starts the investigation (24), even for patients with no respiratory symptoms (i.e. preoperative exams). Some of the classic x-ray findings are described in the Scadding scale but most of all abnormal x-ray findings can relate to sarcoidosis. The clinical presentation is a wide variety of symptoms. Pulmonary cough, dyspnea, shortness of breath, fatigue or night sweats (25). Lymph nodes, mainly hilar adenopathy (95-98%) and also peripheral lymph nodes (10-20%). Cutaneous manifestations are highly prevalent (15%) more commonly erythema nodosum and lupus pernio. Association with uveitis (10-30%) and neuropathy of the facial nerve (5%) are highly suggestive findings (7). Nephrolithiasis and nephrocalcinosis are more prevalent in these patients and the evidence of hypercalcemia (10-17%) e hypercalciuria (67%) are common symptoms and belong to daily practice of the urologist (10, 25, 26).

In the other hand, sarcoidosis is a multiorgan disease and a patient with no pulmonary or lymph nodes may still have sarcoidosis. 10% of patients may not present any of those at first (25), and urological findings have been referred as the first sign for the diagnosis of sarcoidosis in some and renal colic was the first sign of the disease in 2.2% of cases (10). For this, the urologist should always have in the follow-up of his patients the possibility of sarcoidosis in mind and investigate if some other findings start to present, due to a slow onset of symptoms.

In an appropriate clinical setting, the presence of non-necrotizing granulomas with no evidence of infection is the usual criterion to suggest

the diagnosis. Sarcoidosis mimics nonspecific granulomatous reactions. These should be excluded by a careful examination and by medical, occupational, and medication histories. In practice, the disease is most often diagnosed by biopsy of accessible tissues, usually skin, lungs, or peripheral lymph nodes (27). Sarcoidosis is a systemic granulomatous disease and the diagnosis usually requires the demonstration of typical lesions in more than one organ system and it is recommended a histologic diagnosis before commencing any treatment (26). The disease manifestation in several systems and incidence are exposed on Table-1.

Renal sarcoidosis is often accompanied by systemic manifestations although isolated renal sarcoidosis is an accepted entity. The presence of sarcoid-related granulomatous interstitial nephritis is the goal but as related before, the absence of characteristic kidney biopsy findings does not exclude the diagnosis and clinical manifestations with other tissues biopsy should be attempted (13). All patients diagnosed with sarcoidosis should be evaluated for the presence of renal involvement to prevent significant chronic kidney disease (28).

Bronchoscopy is a reliable, minimally invasive technique to diagnose the disease. Combination

Table 1 – Extra pulmonary signs and symptoms of Sarcoidosis.

Organ/System	Prevalence (%)	Simptoms	Investigation
Cutaneous system	15% (9-37%)	Papules, nodules, plaques, scar sarcoidosis, lupus pernio, subcutaneous sarcoidosis	Biopsy
Peripheral lynphnodes	10-20%	Mostly cervical or supraclavicular, inguinal, axillar, epitrochlear or submandibular lymph node sites; painless and mobile	Biopsy
Ocular system	10-30%	Anterior, intermediate, or posterior uveitis, retinal vascular change, conjuntival nodules, lacrimal gland enlargement	Systematics ophtalmologist exam, slit-lamp exam, fluorescein angiography
Hepatic (Gastrointestinal system)	20-30%	Often symptom-free. Abnormal liver function test, hepatomegaly, rarely cholestasis, portal hypertension, hepatic insufficiency	Systematics liver function tests, CT, biopsy
Splenic (Gastrointestinal system)	10%	Splenomegaly; rarely pain, pancytopenia; very rarely, splenic rupture	Echography, CT
Cardiovascular system	2-5%	Atrioventricular or bundle branch block, ventricular tachycardia or fibrillation, congestive heart failure, pericarditis, irmpaiment of sympathetic nerve activity	Eletrocardiography, Echocardiography, BNP, MRI, scintigraphy, FDG PET
Nervous System	5%	Facial nerve palsy, optic neuritis, leptomeningitis, diabetis insipidus, hypopituitarism, seizures, cognitive dysfunction, deficts, hydrocefalus, psychiatric manifestations, spinal cord disease	Cerebrospinal fluid investigation, MRI, hormonal dose, eletromyography, biopsya rarely done
Renal system	5-20%	Increased creatininemia, hypercalcemia, nephrocalcinosis, kidney stones	Systematic renal tests, biopsy

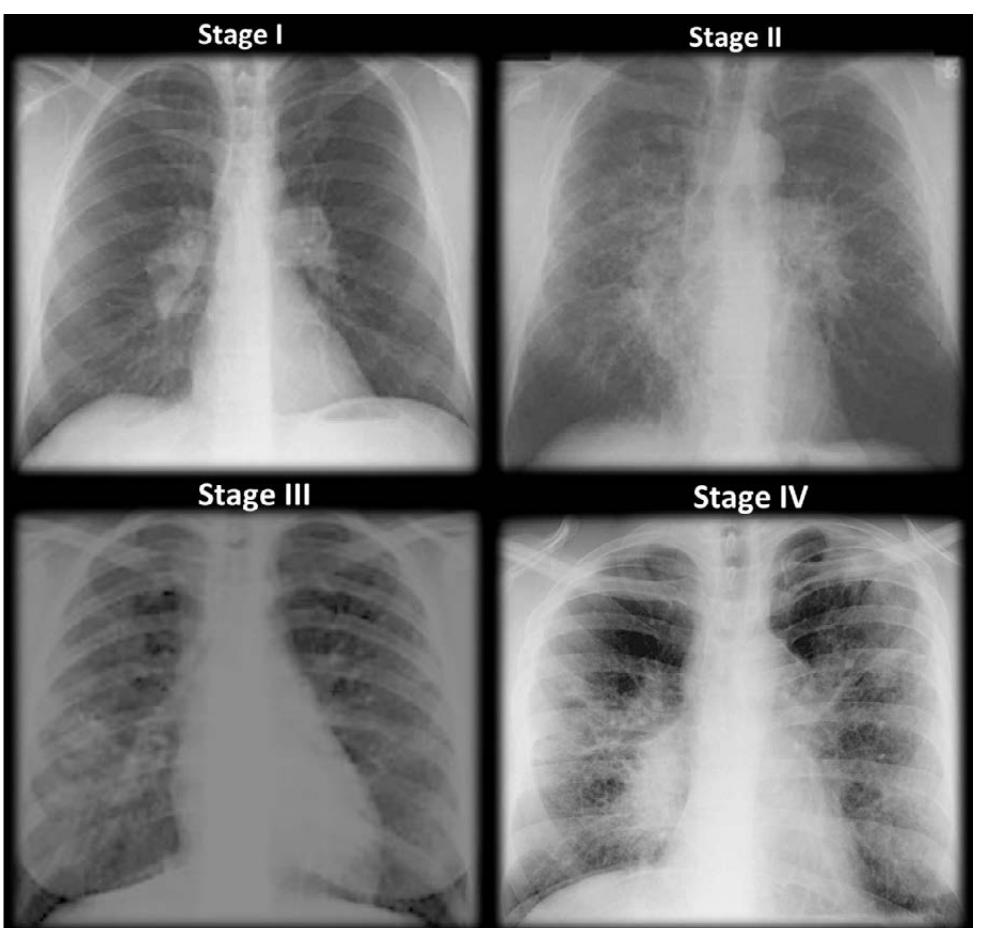
Extrapulmonary investigation
Adapted - Sarcoidosis(25); Management of extrapulmonary sarcoidosis (27).

of transbronchial biopsy with endobronchial (mucosal) biopsy or transbronchial needle aspiration of enlarged lymph nodes increases the sensitivity of the technique to as much as 91%. Endobronchial ultrasonography (with ROSE - Rapid on-site cytological examinations) has been used more recently to further improve diagnostic yield. Samples should be analyzed for infectious agents by appropriate stains, including stains for mycobacteria and fungus, as well as by culture (27).

The Scadding scale, a descriptive schema is widely used to describe chest x-ray finding. It does not represent sequential or temporal disease states, and the predictive ability of the scale allows an approximation of outcomes. It was only described in the 19th century and standardized by the WASOG committee. Types are: 0 (normal radiological findings); I (bilateral mediastinal hilar adenopathy); II (adenopathy and pulmonary infiltrates); III (pulmonary infiltrates only); and IV (pulmonary fibrosis) (25). Features that should prompt consideration of an alternative diagnosis include pleural effusion, unilateral abnormalities, and the presence of calcification in the lymph nodes. Chest CT usually shows typical micronodular infiltrates distributed in a bronchial vascular pattern, often predominating in the mid to upper lung zones (13) (Figure-3).

Other diagnostic modalities for different organs testing may be appropriate and guided by the initial symptoms and examination findings. Routine testing for elevated liver enzymes, hypercalcemia, renal dysfunction, ophthalmologic involvement, and electrocardiographic abnormalities is standard at baseline. Magnetic resonan-

Figure 3 - Scadding scale.



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ce imaging (MRI) with gadolinium or gallium is useful for diagnosing neurologic involvement. Lumbar puncture should be performed in the appropriate clinical context to exclude mycobacterial or fungal infections. Thallium or sesamoid scintigraphy is useful to identify areas of active or inactive myocardial involvement. Newer imaging techniques, such as fluorodeoxyglucose positron emission tomography (FDG-PET) and gadolinium--enhanced MRI are promising modalities for diagnosis and for monitoring treatment response (27).

High levels of angiotensin converting enzyme (ACE) have been reported in sarcoidosis, the frequency varies from 40% up to 90% (2). The enzyme is produced by epithelioid cells, multinucleated giant cells, and macrophages within granulomas (13). It presents a false-negative rate of 40% and false-positive rate of 10%. Other conditions may raise the levels of ACE and might have a differential diagnosis with sarcoidosis such as Leprosy, Myeloma, Gaucher Disease, Amyloidosis, Acute Histoplasmosis, Hyperthyroidism, Hyperparathyroidism, Alcoholic Cirrhosis, Primary Biliary Cirrhosis, Oncogenic Hypercalcemic, Military Tuberculosis, Pulmonary Endothelia Disease, Elverson-Rosenthal syndrome - "Sarcoid-like" granuloma. Therefore, it must be analyzed with criteria but usually consists in more granulomatous impairment, pulmonary or systemic, and might be useful for treatment monitoring as the levels tend to normalize with the spontaneous or corticoid induced remission of the disease (2). Recent data have demonstrated that the presence of certain human leukocyte antigen (HLA) haplotypes (e.g., HLA-DR17 and HLA-DQB1) confers good prognosis in certain European populations (30). However, the usefulness of HLA typing in other populations has not been confirmed (27). A diagnosis algorithm is depicted on Figures 4a and 4b.

Treatment

The initial treatment of sarcoidosis is glucocorticoids, the most effective, rapid-acting and available drug. It's the first line of treatment (31). The therapy significantly improves the clinical manifestations of sarcoidosis and normalizes hypercalcemia and hypercalciuria associated with this disease. Corticosteroids down regulate the activity of 1alphahidroxylase in the pulmonary macrophages and granulomas normalizing the blood and urinary levels of calcium (21). Hypercalciuria can lead to renal failure and the therapy improves renal function (9, 10). There is no standard dose or time for the treatment. It usually starts with low--dose prednisone 20-40mg/day for mild disease or every other day. For major organ impairment, a dose of 1mg/kg/d is usually used. The follow-up is after 1-3 months with the response based on clinical progress, pulmonary radiology and functional status, tapering up to 5mg/week after the initial period (13, 31). Corticosteroids have many well-known side effects, the most important being diabetes, hypertension, osteoporosis and central obesity (32). The medical management of sarcoidosis according to clinical manifestation is resumed on Table-2.

There are no major marks of the disease but ACE (angiotensin-converting enzyme) can be related to disease activity. Usually the treatment is due to 12 months. For advanced cases with no response to corticoids, other cytotoxic drugs may be used such as methotrexate and azathioprine (26). New immunomodulator drugs are being tested for specific cases and study protocols like infliximab and etanercept are on course. Non-responding cases with high calcium levels may benefit with ketoconazole use. In addition, a low calcium diet, adequate hydration, and avoiding exposure to sunlight may prevent deterioration of hypercalcemia and hypercalciuria. Supplements of vitamin D and calcium and calcium rich foods should be avoided (11).

Although not all cases of sarcoidosis present with hypercalcemia, the majority will have this electrolyte disorder. Acute symptomatic hypercalcemia is normally treated in hospital settings with intravenous infusion of normal saline solutions. Loop diuretics need to be added to facilitate urinary calcium excretion via the thick segment of the loop of Henle. Calcitonin is rarely used for acute hypercalcemia owing to its short acting effect on extracellular calcium levels. The use of glucocorticoids is an essential step for the treatment of hypercalcemia related to sarcoidosis as they suppress intestinal absorption of calcium and 1-alfa hydroxylase in sarcoid granulomas (19). Most au-

Figure 4 – Algorithm for diagnosis of Sarcoidosis considering disease criteria (A) and rationale flow chart (B).

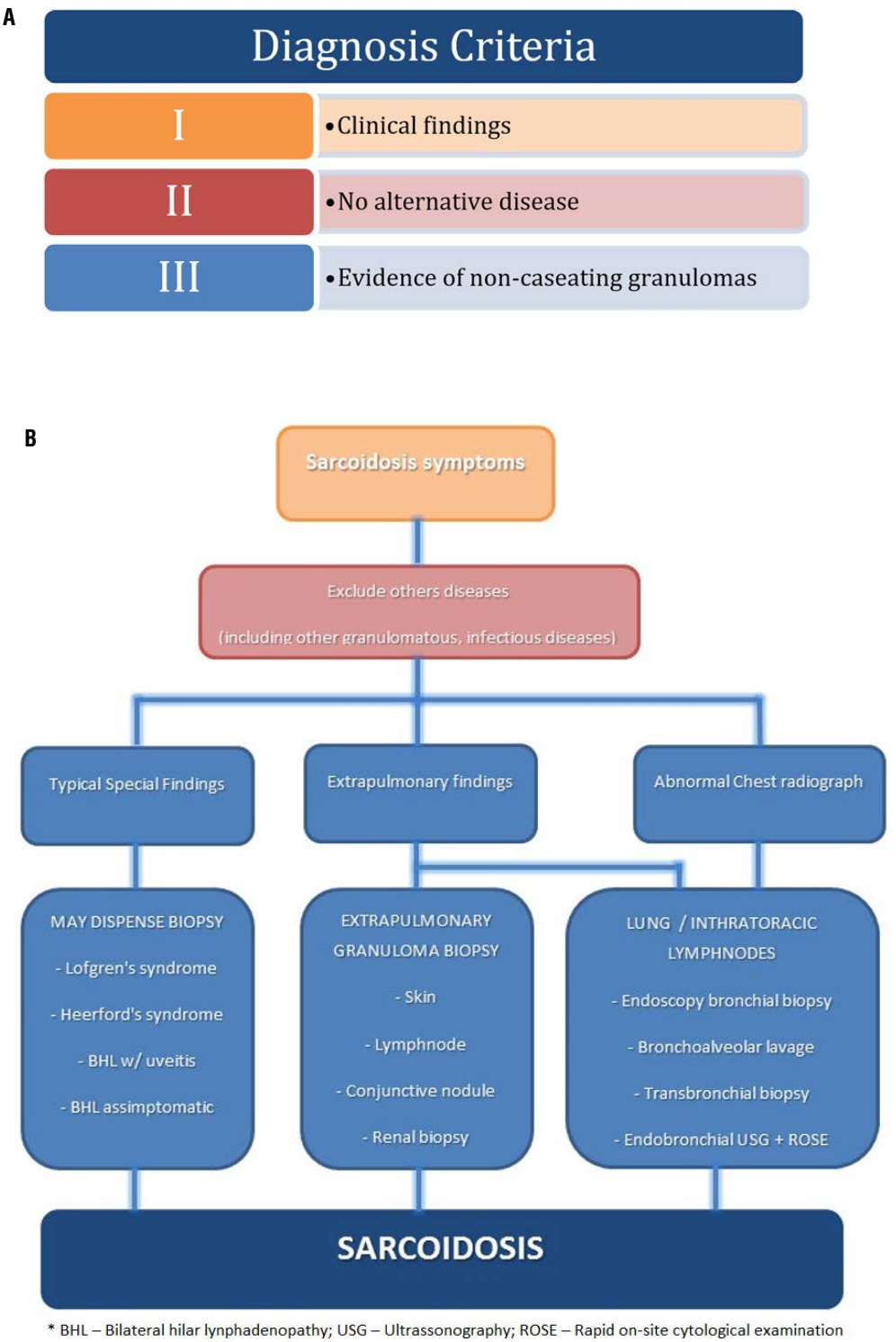

Table 2 – Medical management of Sarcoidosis according to clinical manifestation.

Renal Manifestations	Initial Treatment	Alternative Treatment	Alt. Treatment	Alt. Treatment	Comments
Hypercalcemia Hypercalciuria	Glucocorticoids Initial: 0,3-0,5mg/kg/d Mainteance: 5-10mg/d	Hydroxychloroquine 200-400mg/day	Ketoconazol 200-800mg/day		IV hydration Limit sunlight Low intake calcium, vitD and oxalate Avoid thiazide
Granulomatous Interstitial Nephritis - GIN	Glucocorticoids Major: 1mg/kg/d Mild: 0,5mg/kg/d Mainteance: 5-10mg/d	Azathioprine 2mg/kg/day (50-200mg/d)	Mycophenolate mofetil 1g twice a day (500-3000mg/d)	Infliximab 3-5mg/kg week 0, 2, 6 for 4-8weeks	Add a steroid-sparing agent to the threatment if relapse or dificulty to taper
Glomerular Disease	Glucocorticoids Initial: 1mg/kg/d Mainteance: 5-10mg/d	After GIN alternatives	Methotrexate 10-20mg/week		Folic acid supplementation
Tubular Dysfunction	Glucocorticoids Initial: 1mg/kg/d Mainteance: 5-10mg/d	After GIN alternatives	Methotrexate 10-20mg/week		Folic acid supplementation
Nephrolitiasis	Metabolic control	Surgical threatment of lithiasis			Hypercalcemia and hypercalciuria control
Nephrocalcinosis	Metabolic control				Hypercalcemia and hypercalciuria control Higher rate of renal failure
Treatment					

thors recommend a starting dose of 0.3-0.5mg/kg/day and a maintenance dose of 5-10mg/day with duration of treatment of 12 months (13). Chloroquine with a dose of 200-400mg can be used as an alternative treatment for hypercalcemia and for patients with sarcoidosis who cannot be treated with glucocorticoids. Ketoconazole 200-800mg a day can be utilized as another non-prednisone alternative for the treatment of hypercalcemia (13). The mechanism of action for both drugs is related to the suppression of 1.25 dihydroxy vitamin D production in granulomas.

The use of bisphosphonate for sarcoidosis--related hypercalcemia with elevated plasma 1.25 dihydroxy vitamin D levels was reported to provide a rapid correction of plasma calcium levels without affecting vitamin D concentrations. One has to realize that the use of bisphosphonates will alleviate hypercalcemia, however, it will not influence the disease progression. Evaluation of a 24-h urine collection for calcium excretion is recommended in all patients with sarcoidosis (31). Moreover, learning about the complete metabolic profile of the urine may provide valuable insights in the management of nephrolithiasis related to hypercalcemia and hypercalciuria in these patients. Low dietary intake of calcium, vitamin D, oxalate and avoidance of thiazide-like diuretics (calcium-sparing proprieties) are generally recommended for patients with hypercalcemia. Limiting sunlight exposure is also advised to prevent the enhancement of vitamin D production (13).

Azathioprine - Immunosuppressive drug which can be used as steroid-sparing agent or in patients with failure or a contraindication to corticosteroids. It has a delayed effect, treatment with these drugs should start only after at least 1 month of treatment with glucocorticoids (13). Azathioprine should be given in a daily dose of 2mg/kg (50-200mg/day) and can be used in men and women who want to have children and used during pregnancy (31).

Methotrexate - It is an important agent and a preferred second-line in the treatment of extra-renal sarcoidosis where it can be used as an alternative to corticosteroids or as a steroid-sparing agent (13). Usual dose is of 10-20mg/week orally or intramuscularly (31). The renal excretion makes it not recommended for possible accumulation of the drug and development of major side effects.

Mycophenolate mofetil - Another immunosuppressive for steroid-sparing, with insufficient data but in theory leads to fewer bone marrow toxic effects and less infections than other immunosuppressive agents. The dose starts with 1000mg twice a day (500-3000mg/day) (31). It can improve kidney function previously damaged by the sarcoidosis (13).

TNF-alpha inhibitors - Treatment strategy after steroid-resistant/refractory disease. It should only be used after immunosuppressive agents have been tried (13). Infliximab dose starts from 3-5mg/kg at week 0, 2, 6 and then every 4-8 weeks (31). There is a rapid effect, as early as two weeks and steady improvement of renal function was reported (13). Possible loss of response due to anti-infliximab antibody formation.

Kidney transplantation End-stage renal disease secondary to sarcoidosis is uncommon. The disease generally occurs in young and middle--aged adults. Renal transplantation can be carried out safely in patients with sarcoidosis with excellent graft and patient survival (33). However, a relatively high rate of renal recurrence (17%) after transplantation was reported in most cases occurring shortly after transplantation with negative effect on graft function. The long-term effects of recurrence on graft survival remain elusive. A short delay between the last episode of sarcoidosis and renal transplantation is a risk factor for recurrence as is necessary in other diseases. Relapse after transplantation has been managed with infliximab in a steroid-resistant case (34).

CONCLUSION

Sarcoidosis is considered an “iceberg” disease, from one initial symptom, the physician finds a complete pathology with multiples systems affected. Disordered calcium metabolism and renal involvement should always require treatment given the risk of the development of complications such polyuria, dehydration, kidney stones and even renal failure.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357:2153-65.
2. Fernandes, JC – Estudo das associações clínicas, radiológicas e funcionais em pacientes com sarcoidose: série de casos. Tese de Mestrado UFRGS - 2008.
3. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. 1997;145:234-41.
4. Silva VL, Rufino R, Costa, CHC, Epidemiologia da Sarcoidose no Brasil e no Mundo. Revista Hospital Universitário Pedro Ernest. UERJ. Ano11/2012.
5. Kato Y, Taniguchi N, Okuyama M, Kakizaki H. Three cases of urolithiasis associated with sarcoidosis: a review of Japanese cases. Int J Urol. 2007;14:954-6.
6. La Rochelle JC, Coogan CL. Urological manifestations of sarcoidosis. J Urol. 2012;187:18-24.
7. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, et al. Case Control Etiologic Study of Sarcoidosis (ACCESS) research group. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164(10 Pt 1):1885-9.
8. Bergner R, Hoffmann M, Waldherr R, Uppenkamp M. Frequency of kidney disease in chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2003;20:126-32.

9. Muther RS, McCarron DA, Bennett WM. Renal manifestations of sarcoidosis. Arch Intern Med. 1981;141:643-5.
10. Le Besnerais M, François A, Leroy F, Janvresse A, Levesque H, Marie I. [Renal sarcoidosis: a series of five patients]. Rev Med Interne. 2011;32:3-8.
11. Lebacq E, Desmet V, Verhaegen H. Renal involvement in sarcoidosis. Postgrad Med J. 1970;46:526-9.
12. Berliner AR, Haas M, Choi MJ. Sarcoidosis: the nephrologist's perspective. Am J Kidney Dis. 2006;48:856-70.
13. Hilderson I, Van Laecke S, Wauters A, Donck J. Treatment of renal sarcoidosis: is there a guideline? Overview of the different treatment options. Nephrol Dial Transplant. 2014;29:1841-7.
14. Casella FJ, Allon M. The kidney in sarcoidosis. J Am Soc Nephrol. 1993;3:1555-62.
15. Rizzato G, Colombo P. Nephrolithiasis as a presenting feature of chronic sarcoidosis: a prospective study. Sarcoidosis Vasc Diffuse Lung Dis. 1996;13:167-72.
16. Darabi K, Torres G, Chewaproug D. Nephrolithiasis as primary symptom in sarcoidosis. Scand J Urol Nephrol. 2005;39:173-5.
17. Murphy GP, Schirmer HK. Nephrocalcinosis, urolithiasis and renal insufficiency sarcoidosis. J Urol. 1961;86:702-6.
18. Hannedouche T, Grateau G, Noël LH, Godin M, Fillastre JP, Grünfeld JP, et al. Renal granulomatous sarcoidosis: report of six cases. Nephrol Dial Transplant. 1990;5:18-24.
19. Manthuruthil S, Maroz N. Renal Spectrum of Sarcoidosis. in: Sarcoidosis Diagnosis. 2016.
20. Cheidde L, Ajzen SA, Tamer Langen CH, Christophalo D, Heilberg IP. A critical appraisal of the radiological evaluation of nephrocalcinosis. Nephron Clin Pract. 2007;106:c119-24.
21. Anderson GS, Graham AG. Renal sarcoidosis and nephrolithiasis. Scott Med J. 1960;5:392-6.
22. Longcope WT, Freiman DG. A study of sarcoidosis; based on a combined investigation of 160 cases including 30 autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital. Medicine (Baltimore). 1952;31:1-132.
23. Judson MA, Thompson BW, Rabin DL, Steimel J, Knattereud GL, Lackland DT, et al. The diagnostic pathway to sarcoidosis. Chest. 2003;123:406-12.
24. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164(10 Pt 1):1885-9.
25. Baughman RP. Pulmonary sarcoidosis. Clin Chest Med. 2004;25:521-30, vi.
26. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. 1999;160:736-55.
27. Culviers, Daniel A. Sarcoidosis. Cleveland Clinic. August 2010.
28. Al-Kofahi K, Korsten P, Ascoli C, Virupannavar S, Mirsaeidi M, Chang I, et al. Management of extrapulmonary sarcoidosis: challenges and solutions. Ther Clin Risk Manag. 2016;12:1623-34.
29. Jara-Palomares L, Caballero-Eraso C, Gutiérrez C, Donate A, Rodríguez-Portal JA. Clinical Manifestations of Sarcoidosis, Sarcoidosis, Yoshinobu Eishi, IntechOpen. Available at. <https://www.intechopen.com/books/sarcoidosis/clinical-manifestations-of-sarcoidosis>
30. Sato H, Grutters JC, Pantelidis P, Mizzon AN, Ahmad T, Van Houte AJ, et al. HLA-DQB1*0201: a marker for good prognosis in British and Dutch patients with sarcoidosis. Am J Respir Cell Mol Biol. 2002;27:406-12.
31. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. Lancet. 2014;383:1155-67.
32. Baughman RP, Lower EE. Therapy for extrapulmonary sarcoidosis. Semin Respir Crit Care Med. 2002;23:589-96.
33. Aouizerate J, Matignon M, Kamar N, Thervet E, Randoux C, Moulin B, et al. Renal transplantation in patients with sarcoidosis: a French multicenter study. Clin J Am Soc Nephrol. 2010;5:2101-8.
34. Srivastava S, Rajakariar R, Ashman N, Raftery M, Brown H, Martin JE. Infliximab as long-term maintenance in steroid-resistant and recurrent sarcoidosis in a renal transplant with central nervous system involvement. Clin Kidney J. 2012;5:53-5.

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ORIGINAL ARTICLE

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Computed tomography imaging characteristics of clear cell papillary renal cell carcinoma

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ABSTRACT

Purpose: Clear cell papillary (CCP) renal cell carcinoma (RCC) is a new subtype of RCC that was formally recognized by the International Society of Urological Pathology Vancouver Classification of Renal Neoplasia in 2013. Subsequently, CCP RCC was added to the 2016 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs. In this study, we retrospectively investigated the computed tomography (CT) findings of pathologically diagnosed CCP RCC.
Materials and Methods: This study included 12 patients pathologically diagnosed with CCP RCC at our institution between 2015 and 2017. We reviewed the patient's CT data and analyzed the characteristics.
Results: Nine solid masses and 3 cystic masses with a mean tumor size of 22.7±9.2mm were included. Solid masses exhibited slight hyper-density on unenhanced CT with a mean value of 34±6 Hounsfield units (HU), good enhancement in the corticomedullary phase with a mean of 195±34HU, and washout in the nephrogenic phase with a mean of 133±29HU. The walls of cystic masses enhanced gradually during the corticomedullary and nephrogenic phases. Solid and cystic masses were preoperatively diagnosed as clear cell RCC and cystic RCC, respectively.
Conclusions: The CT imaging characteristics of CCP RCCs could be categorized into either the solid or cystic type. These masses were diagnosed radiologically as clear cell RCC and cystic RCC, respectively.

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INTRODUCTION

Clear cell papillary (CCP) renal cell carcinoma (RCC) is a low-grade renal tumor that was first introduced into the International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia in 2013 (1). Subsequently, this entity was added to the 2016 edition of the World Health Organization (WHO) Classification of Tumors of the Urinary System and Male Genital Organs (2). CCP RCC is an indolent renal epithelial neoplasm characterized by a tubule-papillary structure of bland clear epithelial cells. The cancer cell nuclei exhibit a predominantly linear alignment away from the basement membrane, with low Fuhrman system nuclear grades of 1 or 2. CCP

RCC lacks a sinusoid-like vasculature and thus differs from clear cell RCC. Moreover, the immunophenotypic factors of CCP RCC differ from those of clear cell RCC and papillary RCC (2). Although CCP RCC was initially thought to be limited to cases of end-stage kidney disease, several later reports described this malignancy in non-diseased kidneys (3, 4).

Generally, CCP RCC is diagnosed from surgical specimens following an initial classification as another type of RCC, such as acquired cystic disease of the kidney (ACDK)-associated RCC or cystic RCC, on preoperative imaging studies. As noted above, CCP RCC is a relatively new pathological subtype, and therefore few reports have described the radiological imaging findings of CCP RCC. In a recent study of 28 CCP RCCs, Wang et al. described two types of typical imaging findings, namely a solid mass with relatively low-level enhancement, as seen in papillary RCC, and heterogeneous regions of hyperenhancement, as seen in clear cell RCC (5).

Although a few articles previously described the radiological findings of CCP RCC, the reported studies included relatively small numbers of patients. In this study, we retrospectively investigated the computed tomography (CT) findings of 12 patients pathologically diagnosed with CCP RCC at a single Japanese institution.

MATERIALS AND METHODS

This retrospective study investigated the clinical, pathological and radiological findings of 12 patients who were pathologically diagnosed with CCP RCC between 2015 and 2017 at our institution.

CT images were obtained using a 64-row detector scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) with the following settings: pitch, 0.83; collimation, 0.5mm; reconstruction thickness/interval, 1.0mm/1.0mm and 120kVp with AutomA. Arterial phase images were obtained using a bolus-tracking contrast monitoring system after contrast material injection for 30 seconds. The total iodine dose was 600mg/kg body weight. Enhanced CT scans were performed at 40-, 90- and 300-seconds post-injection with fixed post-contrast timing, which corresponded to the corticomedullary, nephrogenic and excretory phases, respectively. Preoperative CT images were reviewed by at least two radiologists with more than 10 years of experience. For solid masses, the region of interest used to determine the Hounsfield unit (HU) measurement was placed over the area with the greatest attenuation. For cystic masses, the visual enhancement pattern and Bosniak classification were determined.

Pathological specimens were assessed using hematoxylin-eosin and immunohistochemical staining for cytokeratin (CK) 7, cluster of differentiation (CD) 10, α-methylacyl-CoA racemase (AMACR), transcription factor E3 (TFE3), cathepsin K, and carbonic anhydrase (CA) IX. At least two pathologists with 30 years of experience interpreted the results. The tissue slides were evaluated for growth patterns, architecture, and cellular characteristics. Tumors were staged according to the tumor-node-metastasis system (6) and graded according to the Fuhrman classification (7). The pathological types were determined according to the 2016 WHO Classification of Urogenital Tumors (2).

RESULTS

Clinical characteristics

The patient's characteristics are shown in Table-1. During the study period, 894 patients underwent radical or partial nephrectomy at our institution. Of these, 12 Japanese patients (1.3%) with CCP RCC (6 men, 6 women) were identified. These patients had a mean age at diagnosis of 56.3±10.9 years. Kidney tumors were detected incidentally in 9 of 12 patients, while two patients presented with flank pain and one presented with weight loss. Two of 12 patients had end-stage renal disease (ESRD) for which they underwent dialysis. Regarding the surgical procedure, 10 patients underwent partial nephrectomy; the two patients with ESRD underwent radical nephrectomy.

CT imaging

The CT findings are shown in Table-2 and Figures 1, 2 and 3. The mean tumor size was 22.7±9.2mm. Three tumors were exophytic (>50% projection beyond the renal parenchyma) and 9 were endophytic (<50% within the renal parenchyma). Nine and 3 cases involved solid and cystic masses,

Table 1 - Clinical characteristics.

Number of patients	12
Mean range (range) [y]	56.3 ± 10.9 (43-73)
Gender (n, %)	
Male	6 (50)
Female	6 (50)
Clinical presentation (n, %)	
Incidental finding	9 (75)
Flank pain	2 (16.7)
Body weight loss	1 (8.3)
End-stage renal disease (n, %)	2 (16.7)
Surgical procedure (n, %)	
Radical nephrectomy	2 (16.7)
Partial nephrectomy	10 (83.3)

respectively. Regarding CT attenuation, all but one solid mass (exception: case 9) appeared as a mildly hyperdense area on unenhanced CT, with a mean value of 34±6HU. These areas exhibited good enhancement in the corticomedullary phase (CMP) with a mean of 185±45HU, and washout in the nephrogenic phase with a mean of 137±30HU as shown in Figure-1. Case 9 exhibited a solid mass (42HU) with ACDK, which was enhanced in both the corticomedullary phase (101HU) and nephrogenic phase (172HU). As shown in Figures 2 and 3, the walls and septum of small cystic lesions were enhanced gradually in the corticomedullary and nephrogenic phases.

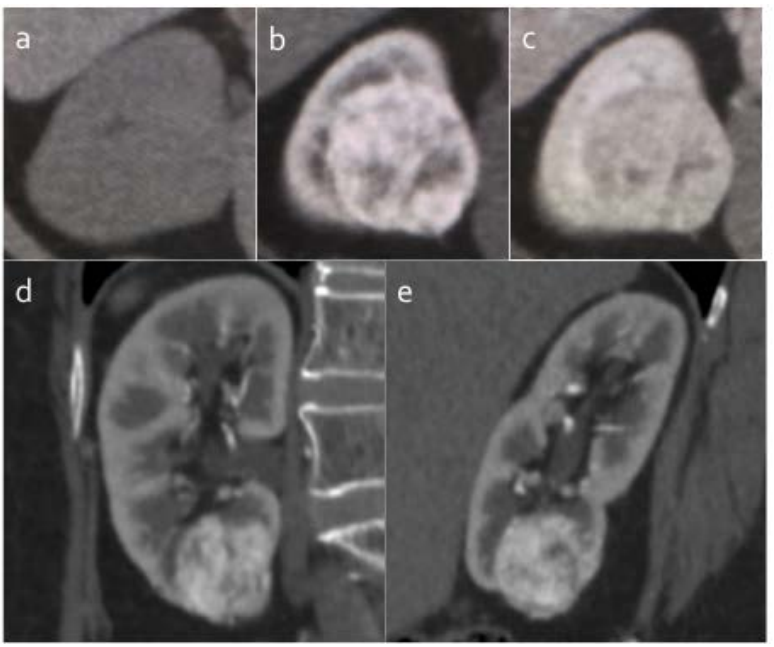
Eight of the 9 patients with solid masses received radiologic diagnoses of clear cell RCC. The ninth patient was diagnosed with ACDK-associated RCC. All patients with cystic masses received radiologic diagnoses of cystic RCC (2 Bosniak III cases and 1 Bosniak IV case).

Table 2. CT imaging characteristics of clear cell papillary renal cell carcinoma.

Case	Age (year)	Sex	Tumor size (mm)	ESRD	CT pattern	Enhanced pattern (HU)			Preoperative diagnosis
						Plain	CMP	Nephrogenic	
1	64	F	12		solid	37	216	150	Clear Cell RCC
2	52	M	21		solid	33	163	143	Clear Cell RCC
3	73	F	30		solid	38	249	187	Clear Cell RCC
4	45	F	28	yes	solid	25	173	94	Clear Cell RCC
5	54	M	16		solid	25	147	105	Clear Cell RCC
6	50	F	12		solid	35	219	118	Clear Cell RCC
7	62	F	20		solid	43	210	139	Clear Cell RCC
8	44	M	19		solid	33	185	129	Clear Cell RCC
9	68	F	28	yes	solid	42	101	172	ACDK associated RCC
10	71	M	13		cystic				Cystic RCC BosniakIV
11	43	M	32		cystic				Cystic RCC Bosniak III
12	49	M	41		cystic				Cystic RCC Bosniak III

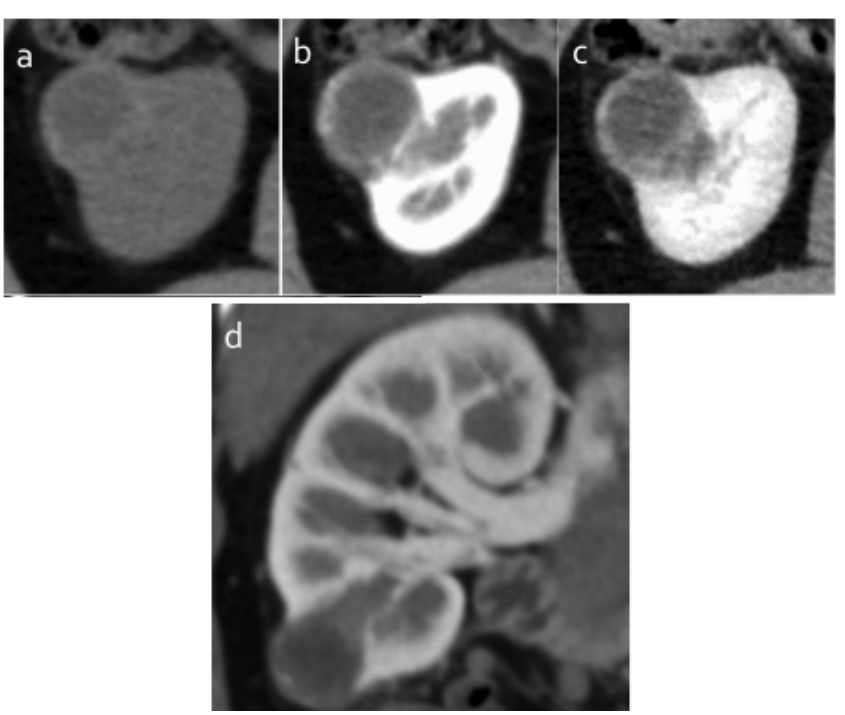
CMP= corticomedullary phase

Figure 1 - Solid pattern: Case 3.



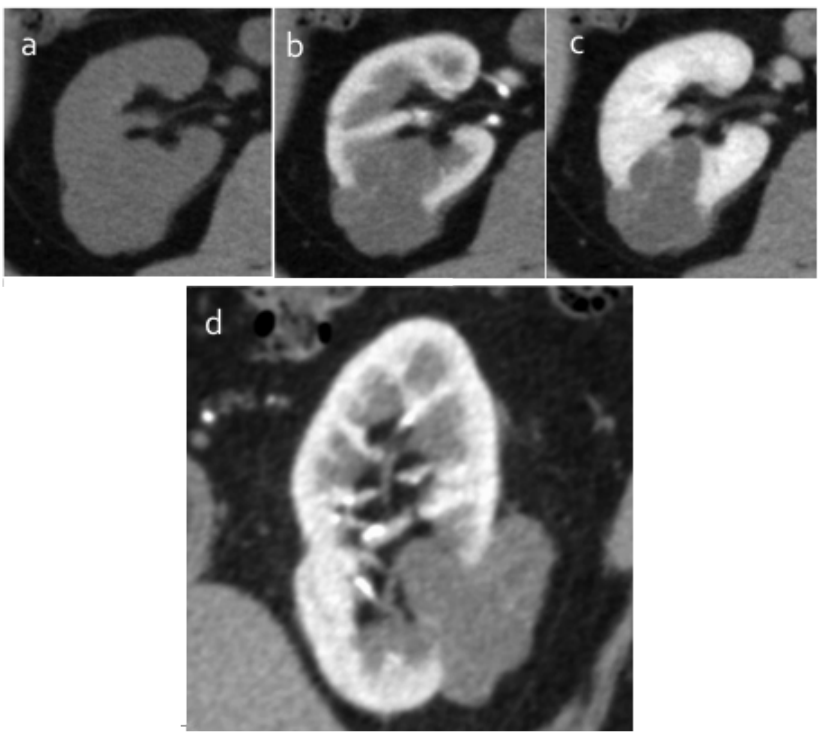
a) Non-enhanced CT: Mild high density area (38HU). **b)** Corticomedullary phase: Well enhanced (249HU). **c)** Nephrogenic phase: Washed out (187HU). **d)** Coronal slice imaging at the corticomedullary phase. **e)** Sagittal slice imaging at the corticomedullary phase.

Figure 2 - Cystic pattern: Case 11.



a) Non-enhanced CT: Mild density cyst. **b)** Corticomedullary phase: Enhanced cyst wall. **c)** Nephrogenic phase: The density of the cyst wall is almost the same with that of CMP. **d)** Coronal slice imaging at the corticomedullary phase.

Figure 3 - Cystic pattern: Case 12.



a) Non-enhanced CT: Mild density cyst. **b)** Corticomedullary phase: Enhanced septum. **c)** Nephrogenic phase: The density of the septum is almost the same with that of CMP. **d)** Coronal slice imaging at the corticomedullary phase.

Histopathological findings

Table-3 summarizes the histopathological findings. The mean tumor size was 19.6±9.9mm. Eleven of 12 tumors were stage pT1a, while the twelfth was pT1b. Four and 8 tumors were classified as grade 1 and 2, respectively. Immunohistochemistry revealed CK7 positivity in all cases and CA-IX positivity in all but one case. However, CD10 positivity was observed in only 5 cases, while AMACR was positive in only one case. TFE3 and cathepsin K were negative in all cases.

DISCUSSION

Our present study findings demonstrate that the radiological characteristics of CCP RCC can be categorized into two types: solid and cystic. Regarding the solid type, most CT scans showed that mildly hyperdense areas in the unenhanced phase were well enhanced in the corticomedullary phase and washed out in the nephrogenic phase, similar to clear cell RCC. All but one solid mass (exception: case 9 with ACDK) were radiologically diagnosed as clear cell RCC. Regarding cystic-type tumors, which were radiologically diagnosed as cystic RCC, the cystic walls of small lesions were gradually enhanced, and the HU values were nearly identical between the corticomedullary and nephrogenic phases. Our study demonstrated that all patients pathologically diagnosed with CCP RCC received radiological diagnoses of different subtypes. Therefore, the preoperative diagnosis of CCP RCC might be difficult.

To our knowledge, only two previous studies described the imaging characteristics of CCP RCC. Wang et al. reported the imaging characteristics of 28 CCP RCCs and demonstrated two types of typical findings, namely a solid mass with relatively low-level enhancement (similar to papillary RCC), and heterogeneous regions of hyper-enhancement (similar to clear cell RCC) (5). CCP RCC shares common pathological features with both clear cell RCC and papillary RCC, including cells with a clear cytoplasm and papillary architectu-

Table 3 - Histopathological findings.

Mean tumor size (range) [mm]	19.6 ± 9.9 (10-43)
Pathological stage (n, %)	
T1a	11 (91.7)
T1b	1 (8.3)
≥T2	0 (0)
Tumor grade (n, %)	
Grade1	4 (33.3)
Grade2	8 (66.7)
Grade3	0 (0)
Grade4	0 (0)
CK7 positive (n, %)	12 (100)
CAIX positive (n, %)	11 (91.7)
CD10 positive (n, %)	5 (41.7)
AMACR positive (n, %)	1 (8.3)

re (8). These common pathological characteristics may be reflected in CT images as both clear cell and papillary RCC enhancement patterns. In contrast, we did not observe any enhancement patterns characteristic of papillary RCC, which might be due to the limited number of patients included in our study. Regarding the distinction of CCP RCC from other RCC subtypes via CT imaging, Mnatzakanian et al. reported the imaging characteristics of 18 CCP RCCs and compared these with the features of clear cell RCC and papillary RCC. They found that compared to papillary RCC, CCP RCC has a lower mean attenuation value on unenhanced CT (≤25HU), ill-defined margins, non-enhancing areas, and hyperintensity on T2-weighted magnetic resonance imaging. However, the authors noted no significant differences in imaging features between CCP RCC and clear cell RCC (9).

In the present study, a pathological analysis of CCP RCC revealed proliferating cells with clear cytoplasm that formed papillo-tubular, acinar, and cystic architectures, as described in the ISUP (1). Eleven and 1 case in the present study were staged as pT1a and pT1b, respectively, and 4 and 8 cases received Fuhrman grades of 1 and 2, respectively. No perirenal or lymphovascular invasion was noted. Taken together, these results further confirm the low malignant potential of CCP RCC (10). Immunohistochemistry can also be useful for distinguishing CCP RCC from other RCC subtypes. Although all RCC tumor cells are positive for PAX8, a marker of renal origin, the distinct immunophenotypic characteristics of CCP RCC include strongly diffuse CK7 and CA-IX expression. CA-IX staining reveals a cup-shaped and membranous distribution pattern with an absence of staining along the luminal borders of tumor cells. However, these cells are consistently negative for CD10, AMACR, cathepsin K and TFE3 (8, 11-15). In our study, CK7 positivity was observed in all cases, and all but one case exhibited CA-IX staining in the basolateral domains of tumor cells, which yielded giving a “cup-shaped” appearance.

In this study, CCP RCC was associated with ESRD in two patients who were submitted to hemodialysis, consistent with other studies (9, 16). As noted previously, CCP RCC was initially reported in patients with ESRD, but was later observed in non-disease settings. Aron et al. discussed the histopathologic features of these latter CPP RCCs and confirmed that this malignancy is a unique subtype of adult renal epithelial neoplasia in which the tumors are frequently small, have a low nuclear grade, and occur in same spectrum ranging from tumors occurring sporadically to those occurring in ESRD (4). In a previous investigation of the pathological characteristics of RCC in 408 patients receiving dialysis, we reported that 76%, 22% and 4% of the patients were diagnosed with cystic RCC, papillary RCC and other types of RCC, respectively (17). Given the relatively recent distinction of CCP RCC, the low-grade nature of this malignancy and the recent inclusion of this tumor in the WHO Classification of Tumors of the Urinary System and Male Genital Organs (2), the pathological distribution of CCP RCC in dialysis patients with RCC may differ following the application of new criteria.

CCP RCC has an excellent prognosis, which may reflect the low malignant potential

(10). Massari et al. reviewed 24 publications that reported follow-up data of 362 patients with CCP RCCs/renal adenomatoid tumors and examined the prognoses and outcomes. Notably, no cases of local recurrence, lymph node or distant metastasis and disease-related death were reported during a mean follow-up duration of 38 months (18). Similarly, we did not observe any recurrences, metastases, or disease-related mortality during a mean follow-up duration of 14±6 months. However, the imaging findings do not always reflect the low malignant potential of CCP RCC according to the pathological findings. According to Wang et al. CCP RCCs exhibited a mean growth of 0.6cm (±0.4cm) during a mean follow-up period of 811 days (5), compatible with the observed growth of other low-stage RCCs (19). Moreover, the imaging-based preoperative diagnosis of CCP RCC may be difficult, as discussed previously. Generally, solid-type CCP RCC is diagnosed radiologically as a clear cell or papillary RCC, according to the enhancement pattern. These growth or radiographic patterns may indicate the need for surgical intervention. However, pre-operative CT-guided biopsy is a good diagnostic option for all RCCs except the cystic type, which may yield an insufficient specimen amount due to cystic fluid (20, 21). Given the low malignant potential of CCP RCC, careful follow-up or minimally invasive treatment (e.g., cryotherapy and radiofrequency ablation) should be considered.

This study had some limitations, including its retrospective nature. Moreover, the generalizability of the results may be affected by the single tertiary care institution setting. Still, CCP RCC was only recently defined, and therefore few reports have described this pathological subtype, particularly with regard to radiological findings. Our results therefore provide a useful reference for the diagnostic imaging of CCP RCC, despite the small sample size.

In conclusion, the CT imaging characteristics of CCP RCCs can be divided into solid and cystic types. Although CCP RCC is considered to have a low malignant potential, it is difficult to distinguish this subtype from other subtypes of RCC based on CT imaging features alone.

ABBREVIATIONS

CCP = clear cell papillary
RCC = renal cell carcinoma
ISUP = International Society of Urological Pathology
WHO = World Health Organization
CT = computed tomography
HU = Hounsfield unit
CK = cytokeratin
CD = cluster of differentiation
AMACR = α-methylacyl-CoA racemase
TFE3 = transcription factor E3
CA = carbonic anhydrase
ESRD = end-stage renal disease
CMP = corticomedullary phase
ACDK = acquired cystic disease of the kidney

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

IRB approved number: 4735

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol. 2013;37:1469-89.
2. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2016;70:93-105.
3. Bhatnagar R, Alexiev BA. Renal-cell carcinomas in end-stage kidneys: a clinicopathological study with emphasis on clear-cell papillary renal-cell carcinoma and acquired cystic kidney disease-associated carcinoma. Int J Surg Pathol. 2012;20:19-28.

4. Aron M, Chang E, Herrera L, Hes O, Hirsch MS, Comperat E, et al. Clear cell-papillary renal cell carcinoma of the kidney not associated with end-stage renal disease: clinicopathologic correlation with expanded immunophenotypic and molecular characterization of a large cohort with emphasis on relationship with renal angiomyoadenomatous tumor. Am J Surg Pathol. 2015;39:873-88.
5. Wang K, Zarzour J, Rais-Bahrami S, Gordetsky J. Clear Cell Papillary Renal Cell Carcinoma: New Clinical and Imaging Characteristics. Urology. 2017;103:136-41.
6. Wittekind C. 2010 TNM system: on the 7th edition of TNM classification of malignant tumors. Pathologe. 2010;31:331-2.
7. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6:655-63.
8. Ross H, Martignoni G, Argani P. Renal cell carcinoma with clear cell and papillary features. Arch Pathol Lab Med. 2012;136:391-9.
9. Mnatzakanian GN, Shinagare AB, Sahni VA, Hirsch MS, Silverman SG. Early-stage clear cell tubulopapillary renal cell carcinoma: imaging features and distinction from clear cell and papillary subtypes. Abdom Radiol (NY). 2016;41:2187-95.
10. Gill S, Kauffman EC, Kandel S, George S, Schwaab T, Xu B. Incidence of Clear Cell Papillary Renal Cell Carcinoma in Low-Grade Renal Cell Carcinoma Cases: A 12-Year Retrospective Clinicopathologic Study From a Single Cancer Center. Int J Surg Pathol. 2016;24:207-12.
11. Reuter VE, Tickoo SK. Differential diagnosis of renal tumours with clear cell histology. Pathology. 2010;42:374-83.
12. Rohan SM, Xiao Y, Liang Y, Dudas ME, Al-Ahmadie HA, Fine SW, et al. Clear-cell papillary renal cell carcinoma: molecular and immunohistochemical analysis with emphasis on the von Hippel-Lindau gene and hypoxia-inducible factor pathway-related proteins. Mod Pathol. 2011;24:1207-20.
13. Tickoo SK, Reuter VE. Differential diagnosis of renal tumors with papillary architecture. Adv Anat Pathol. 2011;18:120-32. Erratum in: Adv Anat Pathol. 2015;22:281.
14. Williamson SR, Eble JN, Cheng L, Grignon DJ. Clear cell papillary renal cell carcinoma: differential diagnosis and extended immunohistochemical profile. Mod Pathol. 2013;26:697-708.
15. Deml KF, Schildhaus HU, Compérat E, von Teichman A, Storz M, Schraml P, et al. Clear cell papillary renal cell carcinoma and renal angiomyoadenomatous tumor: two variants of a morphologic, immunohistochemical, and genetic distinct entity of renal cell carcinoma. Am J Surg Pathol. 2015;39:889-901.
16. Zhou H, Zheng S, Truong LD, Ro JY, Ayala AG, Shen SS. Clear cell papillary renal cell carcinoma is the fourth most common histologic type of renal cell carcinoma in 290 consecutive nephrectomies for renal cell carcinoma. Hum Pathol. 2014;45:59-64.
17. Hashimoto Y, Takagi T, Kondo T, Iizuka J, Kobayashi H, Omae K, et al. Comparison of prognosis between patients with renal cell carcinoma on hemodialysis and those with renal cell carcinoma in the general population. Int J Clin Oncol. 2015;20:1035-41.
18. Massari F, Ciccarese C, Hes O, Michal M, Caliò A, Fiorentino M, et al. The Tumor Entity Denominated "clear cell-papillary renal cell carcinoma" According to the WHO 2016 new Classification, have the Clinical Characters of a Renal Cell Adenoma as does Harbor a Benign Outcome. Pathol Oncol Res. 2018;24:447-56.
19. Crispen PL, Viterbo R, Fox EB, Greenberg RE, Chen DY, Uzzo RG. Delayed intervention of sporadic renal masses undergoing active surveillance. Cancer. 2008;112:1051-7.
20. Leveridge MJ, Finelli A, Kachura JR, Evans A, Chung H, Shiff DA, et al. Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. Eur Urol. 2011;60:578-84.
21. Volpe A, Mattar K, Finelli A, Kachura JR, Evans AJ, Geddie WR, et al. Contemporary results of percutaneous biopsy of 100 small renal masses: a single center experience. J Urol. 2008;180:2333-7.

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ORIGINAL ARTICLE

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Prostate cancer screening among elderly men in Brazil: should we diagnose or not?

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ABSTRACT

Purpose: Prostate cancer screening in the elderly is controversial. The Brazilian government and the National Cancer Institute (INCA) do not recommend systematic screening. Our purpose was to assess prevalence and aggressiveness of prostate cancer in men aged 70 years and above, on the first Latin American database to date.
Materials and Methods: Cross-sectional study (n=17,571) from 231 municipalities, visited by Mobile Cancer Prevention Units of a prostate-specific antigen (PSA) based opportunistic screening program, between 2004 and 2007. The criteria for biopsy were: PSA>4.0ng/ml, or PSA 2.5-4.0ng/ml with free/total PSA ratio ≤15%, or suspicious digital rectal examination findings. The screened men were stratified in two age groups (45-69 years, and ≥70 years). These groups were compared regarding prostate cancer prevalence and aggressiveness criteria (PSA, Gleason score from biopsy and TNM staging).
Results: The prevalence of prostate cancer found was 3.7%. When compared to men aged 45-69 years, individuals aged 70 years and above presented cancer prevalence about three times higher (prevalence ratio 2.9, p<0.01), and greater likelihood to present PSA level above 10.0ng/ml at diagnosis (odds ratio 2.63, p<0.01). The group of elderly men also presented prevalence of histologically aggressive disease (Gleason 8-10) 3.6 times higher (p<0.01), and 5-fold greater prevalence of metastases (PR 4.95, p<0.05).
Conclusions: Prostate cancer screening in men aged over 70 may be relevant in Brazil, considering the absence of systematic screening, higher prevalence and higher probability of high-risk disease found in this age range of the population studied.

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INTRODUCTION

Prostate cancer (PCa) is a major issue in cancer incidence and mortality worldwide (1). In the United States of America (USA), the Surveillance, Epidemiology and End Results Program (SEER) data estimated 161.360 new cases of PCa in 2017 (incidence rate 119.8/100.000) (2). PCa is the most commonly diagnosed non-skin neoplasm in American males, and also the third leading cause of cancer death in men (3).

Despite that numbers, the effects of prostate-specific antigen (PSA) screening on mortality are controversial. The two large prospective randomized trials showed conflicting results. The European Randomized Study of Screening for

Prostate Cancer (ERSPC) found a 27% relative reduction in PCa mortality in the intervention arm (4). On the other hand, the Prostate, Lung, Colorectal and Ovarian cancer screening study (PLCO) found no benefits (5). Recent analyses on these data reported PLCO methodological flaws, dismissing its capability of evaluating systematic screening effectiveness. The current US Prevention Services Task Forces draft recommendation states that screening reduces mortality, in spite of harms associated with overdiagnosis and overtreatment (6, 7). There is consensus among medical entities about performing PCa screening only in individuals with life expectancy superior to 10 years (7-9), due to the long cancer-specific survival after the diagnosis of localized disease (10).

Although there are recommendations against PCa screening over the age of 70 (7, 8), some epidemiologic and biologic phenomena justify the investigation of PCa assessment in this population group. First, the age shift: many authors reported demographic changes observed in the last decades in developed countries, where the increment in longevity leads to increasing incidence of senescence-related diseases, like PCa (11). Second, PCa epidemiology: this neoplasm still predominates in the elderly, although PSA screening increased the detection of PCa in younger men. In USA, 57.4% of the new diagnoses were made in men aged ≥65 (2). The literature is still scarce concerning screening in this specific age range. ERSPC (4) and PLCO (5) included few men aged ≥70, and none ≥75. Third, the disease seems to present more unfavorable features when diagnosed in older men: Brassell et al. reported that the clinical and pathological characteristics of PCa worsen with ageing, and men aged ≥70 had worse overall- and cancer-specific survival when compared to younger men (12).

In Brazil, PCa is also a public health problem (13), but data assessing screening are limited, and underprivileged people have difficult access to specialized healthcare system. Unlike many developed countries, systematic screening (defined by PSA testing, with or without digital rectal examination, on a time-regular and age-interval defined basis) has never been performed in the Brazilian population (14). It is important to highlight that, although Brazil follows the trends of age shift (13, 15), the government and the National Cancer Institute (INCA) recommend against systematic PCa screening (16), in opposition to the Brazilian Society of Urology (SBU) favorable recommendations. Considering that scenario, we hypothesized that individuals aged over 70 years and not previously screened may present more aggressive disease at diagnosis.

OBJECTIVES

To test the hypothesis that elderly men (aged 70 and above) of a Brazilian population not exposed to previous systematic screening have increased prevalence of prostate cancer and worse aggressiveness criteria at diagnosis, compared to younger men.

MATERIALS AND METHODS

We performed an analysis on the database of the Mobile Cancer Prevention Units (MCPU) program (14), which visited 231 cities of six Brazilians states between 2004 and 2007, including 17.571 volunteers for PSA-based PCa screening, aged ≥45 years. There was no upper age cut-off on those willing to volunteer, as reported by Faria et al. (14, 17, 18).

The criteria for prostate biopsy were: suspicious digital rectal examination (DRE) findings, or PSA >4.0ng/ml, or PSA 2.5-4.0ng/ml with free/total PSA ratio ≤15% (which was performed to assess the increase in the PCa detection rate in one preliminary study of the MCPU program, when the literature lacked data to the date) (18).

The initial biopsy protocol consisted of transrectal ultrasound (TRUS) guided sextant biopsies. The protocol was changed in November 2004 to mean 14 cores (eventually with additional samples of suspicious areas on TRUS or DRE).

Men with a positive biopsy were clinically staged by magnetic resonance imaging and conventional bone scan. The TNM staging (6th ed.), Gleason score histologic classification (score 2-10 to date) and D'Amico risk stratification systems were utilized.

All men with Gleason score 2-6 (to the date) were considered in the same category "Gleason 2-6" in our study, which currently corresponds to the International Society of Urologic Pathology - ISUP grade group 1 (19).

The whole health care, from screening to treatment, was provided through the public health system at the Barretos Cancer Hospital (BCH).

Study design

A cross-sectional study was performed on the database. The screened men were stratified in two age groups (45-69 years, and ≥70 years). These groups were compared regarding PCa prevalence, previous PSA testing and aggressiveness criteria like PSA levels, Gleason score from biopsy and clinical TNM staging, as well as other relevant variables. The present study protocol was reviewed and approved by the ethics committee of the Hospital das Clinicas of the Ribeirao Preto Medical School of University of Sao Paulo (n. 1.639.824).

Statistical analysis

We used the Statistical Package for Social Sciences software version 17.0 (SPSS, Chicago, IL) for the statistical analysis, using χ^2 (chi-square) tests and Bonferroni correction. According to the study's cross-sectional design, the preferential measure of association utilized was the prevalence ratio (PR). When appropriate, we also calculated the odds ratio (OR). The significance level considered was $p < 0.05$ for all tests.

RESULTS

Age, PSA levels and previous PSA testing

The population studied included 17.571 men with median age of 60 years (range 45-98) and mean PSA level of 2.0ng/ml [SD 6.1, CI95% (1.9-2.1)], 5.108 individuals (29.1%) had at least one previous PSA testing. The median age of men diagnosed with PCa was 68 years.

Group A (age 45-69) enrolled 14.287 men, with median age of 58 years (63 years in men with PCa), mean PSA level of 1.6ng/ml [SD 3.5, CI95% (1.52-1.64)] and 28.2% of men with previous PSA testing.

Group B (age ≥70) accounted 3.284 men, with median age of 74 years (the same in men with PCa of this group), mean PSA level of 3.9ng/ml [SD 11.8, CI95% (3.5-4.3)] and 32.7% of previous PSA testing.

The prevalence of previous screening was 15.7% higher in men aged ≥70 [PR 1.157, CI95% (1.1-1.2), $p < 0.05$], but there was no difference when we compared only men with positive biopsies [PR 1.2, CI95% (0.9-1.5), p=0.11].

PSA levels and PSA range stratification in men with positive biopsies

Considering only PCa cases, the mean PSA level in our sample was 12.7ng/ml [SD 23.8, CI95% (10.9-14.6)]. The mean PSA levels were higher in the group of men aged ≥70: the mean PSA level of group A was 9.5ng/ml [SD 13.2, CI95% (8.2-10.9)], while mean PSA level of group B was 17.3ng/ml [SD 33.0, CI95% (13.3-21.2)].

PSA levels were in higher ranges in the group of elderly men, when compared to the group of age 45-69: PCa cases in the group of elderly men were 92% more likely to present with PSA levels within the 4-10ng/ml range [OR 1.92, CI95% (1.3-2.9), $p < 0.01$], and 2.6 times more likely of being diagnosed within the PSA range above 10ng/ml [OR 2.63, CI95% (1.7-4.0), $p < 0.01$].

Prostate biopsy results and prostate cancer prevalence

Two thousand eight hundred and forty-one men were called for specialized evaluation at the BCH (16.2% of the sample). 2.291 individuals showed up (80.6% of the invited) with 1.647 men biopsied (58% of the invited). The criterion "PSA >4ng/ml" accounted for 51% of the biopsies performed. The distribution of the other criteria was: abnormal DRE (19.7%), both altered PSA and DRE (7.1%), and free/total PSA ≤15% (18.3%).

The overall prevalence of PCa in our study was 3.7%, and the biopsy positivity rate was 39.6%, as shown in Table-1. The group of men aged ≥70 presented a prevalence of PCa three times higher than those aged 45-69 [PR 2.9, CI95% (2.5-3.4), $p<0.05$].

Table 1 - Prostate biopsy results and prostate cancer prevalence.

	Total	Group A (age 45-69)	Group B (age ≥70)	PR	p	CI95%
Biopsied men, n (prevalence)	1,647 (9.4%)	1,088 (7.6%)	559 (17%)	2.24	<0.01	(2.0-2.5)
PCa cases, n (prevalence)	652 (3.7%)	382 (2.7%)	270 (8.2%)	2.9	<0.01	(2.5-3.4)
Biopsy positivity rate	39.6%	35.1%	48.3%	1.38	<0.01	(1.2-1.5)
Total, n	**17,571**	**14,287**	**3,284**	-	-	-

Abbreviations: **PR =** prevalence ratio; p = p value; **CI95% =** confidence interval 95%; **n =** number of men; **PCa =** prostate cancer

Gleason score

The prevalence of histologically aggressive disease (Gleason score 8-10) was higher in the group of elderly men [PR 3.6, CI95% (1.9-6.7), p <0.01], as demonstrated in Table-2.

TNM staging

In our sample, 93.4% of men with PCa presented with localized disease (T1/T2). There was no significative difference between the groups, regarding T2-T4 staging and lymph node staging, as shown in Table-3. Metastatic disease was almost five times more prevalent in men aged above 70 years [PR 4.9, CI95% (1.6-14.9), p <0.05].

D'Amico risk classification stratification

The stratification by the D'Amico risk classification demonstrated that considering the PCa cases, 377 of 652 men (57.8%) presented with intermediate- and high-risk disease. In the group of men aged 45-69 years, 50.8% of PCa cases were intermediate- and high-risk disease at diagnosis. In group B (aged ≥70), 67.7% of PCa cases presented with intermediate- and high-risk.

The analyses of prevalence showed that in the group of men aged ≥70, the prevalence of intermediate-risk PCa was 3.6 times higher [PR 3.6, CI95% (2.8-4.6), p <0.01], and the prevalence of high-risk disease was 5.4 times higher [PR 5.4, CI95% (3.8-7.7), p <0.01] when compared to group A, as seen in Table-4.

DISCUSSION

Our literature review found relevant studies with concordant results. In 2015, Muralidhar et al. published a retrospective paper utilizing SEER data (n=383.039), showing positive association between advanced age and worse Gleason scores, as well as progressively greater proportions of patients with high-risk disease in older age ranges (20). One hypothesis is the drop in testosterone levels in senior men, possibly associated with more aggressive disease (21). Other plausible reason for this phenomenon is the proliferation of undifferentiated cells that represented only a small fraction of the tumoral volume at the beginning of the disease and had time to multiply over

Table 2 - Gleason score from biopsy.

	Total	Group A (age 45-69)	Group B (age ≥70)	PR	p	CI95%
Gleason 2-6, n (%)	440 (67.5%)	276 (72.2%)	164 (60.8%)	0.8	<0.01	(0.7-0.9)
Gleason 7, n (%)	166 (25.5%)	93 (24.4%)	73 (27%)	1.1	0.06	(0.8-1.4)
Gleason 8-10, n (%)	46 (7%)	13 (3.4%)	33 (12.2%)	3.6	<0.01	(1.9-6.7)

Abbreviations: **PR =** prevalence ratio; **p =** p value; **CI95% =** confidence interval 95%; **n =** number of men

Table 3 - TNM Staging.

	Total	Group A (age 45-69)	Group B (age ≥70)	PR	p	CI95%
cT						
T1, n (%)	498 (76.4%)	305 (79.8%)	193 (71.5%)	0.9	<0.05	(0.82-0.98)
T2, n (%)	111 (17.0%)	56 (14.7%)	55 (20.4%)	1.39	0.09	(0.99-1.9)
T3, n (%)	40 (6.1%)	20 (5.2%)	20 (7.4%)	1.42	0.09	(0.8-2.6)
T4, n (%)	3 (0.5%)	1 (0.3%)	2 (0.7%)	2.83	0.09	(0.3-31.1)
cN						
N0, n (%)	624 (95.7%)	371 (97.1%)	253 (93.7%)	0.96	0.05 (NS)	(0.9-1.0)
N1, n (%)	26 (4.0%)	11 (2.9%)	15 (5.6%)	1.98	NS	(0.9-4.2)
cM						
M0, n (%)	634 (97.2%)	378 (99.0%)	256 (94.8%)	0.96	<0.05	(0.93-0.99)
M1, n (%)	18 (2.8%)	4 (1.0%)	14 (5.2%)	4.95	<0.05	(1.6-14.9)

Abbreviations: **TNM =** Tumor-Node-Metastasis; **PR =** prevalence ratio; **p =** p value; **CI95% =** confidence interval 95%; **c =** clinical; **n =** number of men; **NS =** not statistically significant

Table 4 - D'Amico risk stratification comparison of prevalence by groups.

	Total	Group A (age 45-69)	Group B (age ≥70)	PR	p	CI95%
Low, n (prevalence)	275 (1.6%)	188 (1.3%)	87 (2.7%)	2.0	<0.01	1.6-2.6
Intermediate, n (prevalence)	256 (1.5%)	140 (1.0%)	116 (3.5%)	3.6	<0.01	2.8-4.6
High, n (prevalence)	121 (0.7%)	54 (0.4%)	67 (2.0%)	5.4	<0.01	3.8-7.7
PCa cases, n (prevalence)	652 (3.7%)	382 (2.7%)	270 (8.2%)	2.9	<0.01	(2.5-3.4)
Total, n	17,571	14,287	3,284	-	-	-

Abbreviations: **PR =** prevalence ratio; **p =** p value; **CI95% =** confidence interval 95%; **n =** number of men; **PCa =** prostate cancer

time. Other studies also reported the association of older age with more aggressive disease and worse outcomes (22). Of note, Sun et al. reported in a retrospective cohort similar findings in patients aged ≥70, while interestingly demonstrating a migration in T staging as time passed after the PSA era: in the first years of the screening, the tumoral volume, pT staging and PSA levels were higher, but there was no difference in Gleason score along the period studied, suggesting that the PSA screening impacted on the neoplastic growth without affecting its biology (23).

The median age at diagnosis found in our sample was 68 years, similar to the USA's National Cancer Institute data (66 years) (2). Nevertheless, we studied a population in a scenario of low socioeconomic status and poor access to specialized medical assistance, which is suggested by the fact that only 29% of the men had any previous PSA testing, reflecting the low frequency of PCa screening in the Brazilian population. These low rates of early diagnosis and treatment in the areas studied may have led to data reflecting the actual natural history of the disease. We also observed that only 32.6% of men aged ≥70 had at least one previous PSA measurement, so that more than two thirds of those men had not been evaluated over the age range when screening may be more beneficial. The "contamination rate" by previous PSA testing in our study was low, when compared to the literature: ERSPC reported rates around 25% (4). PLCO reported a 40% rate in the control arm at the first year (24), and recent analyses of a rate of contamination of 90% in control group par-

ticipants led the PLCO authors to interpret their results as "no benefit of organized versus opportunistic screening" (5-7). It shows the difficulty in selecting homogeneous samples for prospective trials with long follow-up.

It is notable that 26.8% of men in our study were called for biopsy due to an altered DRE. This rate was superior to the 18% reported by Richie et al. in 1993, at the beginning of the PSA era (25). It may be a consequence of the low screening rate in Brazil, as by definition DRE detects tumors with volume superior to T1c cases (26), more often found in countries where early detection policies were implemented long ago.

The overall biopsy positivity rate in our study was 39.6%. It was 38% higher in the group of men aged ≥70 (PR 1.38). Although comparisons are difficult to draw, these values are superior to the 25% positivity rate found in ERSPC (4). This increase in the biopsy positivity rate associated with ageing goes along with the literature. Increasing positivity rate has been reported in elderly men, reaching 81% in men aged 80 or more (27). Our results demonstrated that men aged ≥70 had a threefold increase in PCa prevalence (PR 2.9) compared to younger men. This finding is in agreement with the well-established concept of increasing PCa prevalence associated with ageing reported in autopsy studies (28).

Our results showed that, when compared to the younger age range, PCa cases among men aged ≥70 had higher mean PSA levels and in higher ranges, with greater probability of presenting with PSA >10ng/ml (OR 2.63), which means increased chance of intermediate- and high-risk disease at diagnosis. This finding is probably linked with the markedly higher prevalence of unfavorable histological biopsy results (Gleason ≥8) in the group of elderly men (PR 3.6), which is also concordant with previous studies (29).

There was no significative difference in the T2-T4 and N1 staging between the age groups studied. However, we found that men aged ≥70 with PCa had a 5-fold chance of presenting with metastatic disease (PR 4.9). The natural history of PCa shows that 5-year survival lowers considerably in patients with M1 disease (2).

As expected, in our study the results of PSA, clinical staging and Gleason score were linked with concordant and statistically significant findings in the D'Amico risk stratification (Table-4). The prevalence of intermediate- and high-risk PCa at diagnosis was substantially higher in men aged ≥70 (PR 3.6 and 5.4, respectively), which is very relevant considering that in advanced stages progression and death due to PCa are more likely, as well as the costs of medical assistance rise and quality of life declines, so these men in theory could have benefits with screening and treatment (2, 12, 23).

Some limitations of our study must be taken into consideration. Although it demonstrated worse clinical, laboratorial and pathological features of PCa in men aged ≥70, its retrospective design does not allow recommending the systematic mass screening on this age range. Also, despite our large sample, the opportunistic screening performed may have led to a selection bias, due to the following reasons:

A) The volunteer individuals enrolled were possibly more motivated to detect the disease, which may not be true to the general population. Those motivated people might be more cautious with their own health, and that may impact outcomes.

B) The areas studied were poor, possibly with a frequency of the analyzed variables different from the whole Brazilian population, if we considered more privileged areas. The Brazilian Society of Urology reported a related phenomenon: poorer people treated in public Brazilian hospitals had older age, higher PSA levels and more metastatic disease at diagnosis (30).

Furthermore, the high ethnic miscegenation in Brazil is a relevant issue, considering that African-descendent populations might behave quite differently from Caucasians (2, 3), providing matter for further research.

To our knowledge, there are no Brazilian papers about PCa screening in this age range. Published literature studied mainly American and European populations. Therefore, this is the first study in Latin America assessing PCa screening in elderly men, concerning the Brazilian reality.

Considering the lack of systematic screening (which is important to emphasize that is not recommended by the government and INCA), our findings may support the concept that screening in men aged over 70 years and life expectancy of at least 10 years may be relevant in Brazil, regarding public health policies and personalized medicine.

CONCLUSIONS

Our study demonstrated a higher prevalence of prostate cancer and a more aggressive pattern of the disease in the age group above 70 years when compared to younger men: higher PSA levels, undifferentiated Gleason score and metastatic dissemination more prevalent, as well as a higher prevalence of intermediate- and high--risk disease at diagnosis.

ABBREVIATIONS

BCH = Barretos Cancer Hospital
c = clinical (TNM staging)
CI95% = confidence interval 95%
DRE = digital rectal examination
ERSPC = European Randomized Study of Screening for Prostate Cancer
INCA = Brazil's National Cancer Institute
M = M staging
MCPU = Mobile Cancer Prevention Units
n = number (of men)
N = N staging.
NS = not statistically significant
OR = odds ratio
p = p value
PCa = prostate cancer
PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening study
PR = prevalence ratio
PSA = prostate-specific antigen
SD = standard deviation
SEER = Surveillance, Epidemiology and End Results Program
T = T staging
TNM = Tumor-Node-Metastasis
TRUS = transrectal ultrasound
USA = United States of America

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87-108.
2. National Cancer Institute: SEER Cancer Statistics Factsheets: Prostate Cancer. 2017. Available at. <http://seer.cancer.gov/statfacts/html/prost.html>.
3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7-30.
4. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014;384:2027-35.
5. Pinsky PF, Prorok PC, Yu K, Kramer BS, Black A, Gohagan JK, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer. 2017;123:592-9.
6. Tsodikov A, Gulati R, Heijnsdijk EAM, Pinsky PF, Moss SM, Qiu S, et al. Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials. Ann Intern Med. 2017;167:449-55.
7. U.S. Preventive Services Task Force: Draft Recommendation Statement: Prostate Cancer: Screening. 2017. Available at. <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening1>
8. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA Guideline. J Urol. 2013;190:419-26.
9. Krahn MD, Bremner KE, Asaria J, Alibhai SM, Nam R, Tomlinson G, et al. The ten-year rule revisited: accuracy of clinicians' estimates of life expectancy in patients with localized prostate cancer. Urology. 2002;60:258-63.
10. Horan AH, McGehee M. Mean time to cancer-specific death of apparently clinically localized prostate cancer: policy implications for threshold ages in prostate-specific antigen screening and ablative therapy. BJU Int. 2000;85:1063-6.
11. Heinzer H, Steuber T. Prostate cancer in the elderly. Urol Oncol. 2009;27:668-72.
12. Brassell SA, Rice KR, Parker PM, Chen Y, Farrell JS, Cullen J, et al. Prostate cancer in men 70 years old or older, indolent or aggressive: clinicopathological analysis and outcomes. J Urol. 2011;185:132-7.

13. Instituto Nacional do Câncer/Brasil: Estimativas para o ano de 2016 das taxas brutas de incidência por 100 mil habitantes e do número de casos novos de câncer, segundo sexo e localização primária, 2016. Available at. <http://www.inca.gov.br/estimativa/2016/sintese-de-resultados-comentarios.asp>.
14. Faria EF, Carvalhal GF, Vieira RA, Silva TB, Mauad EC, Carvalho AL. Program for prostate cancer screening using a mobile unit: results from Brazil. Urology. 2010;76:1052-7.
15. Instituto Brasileiro de Geografia e Estatística: Indicadores sócio demográficos e de saúde no Brasil: 2009. Available at. <http://biblioteca.ibge.gov.br/visualizacao/livros/liv42597.pdf>. Accessed on: Nov 06, 2016.
16. Ministério da Saúde/Brasil. Nota técnica conjunta N. 001/2015. 2015. Available at. <http://www2.inca.gov.br/wps/wcm/connect/9e6e07004a50eca8968bd6504e7bf539/Nota+Técnica+CAP+finalizada.pdf?MOD=AJPERES&CACHEID=9e6e07004a50eca8968bd6504e7bf539>. Accessed 17 Nov 2018.
17. Faria EF, Carvalhal GF, Vieira RA, Silva TB, Mauad EC, Tobias-Machado M, et al. Comparison of clinical and pathologic findings of prostate cancers detected through screening versus conventional referral in Brazil. Clin Genitourin Cancer. 2011;9:104-8.
18. Faria EF, Carvalhal GF, dos Reis RB, Tobias-Machado M, Vieira RA, Reis LO, et al. Use of low free to total PSA ratio in prostate cancer screening: detection rates, clinical and pathological findings in Brazilian men with serum PSA levels <4.0ng/mL. BJU Int. 2012;110(11 Pt B):E653-7.
19. Moul JW: Prostate. AJCC Cancer Staging Manual 8th edition. 2018. Available at. <https://cancerstaging.org/CSE/Physician/Documents/AJCC_PPT%20-Prostate%20Handout%20v2.pdf>. Accessed on: 2019.
20. Muralidhar V, Ziehr DR, Mahal BA, Chen YW, Nezolosky MD, Viswanathan VB, et al. Association Between Older Age and Increasing Gleason Score. Clin Genitourin Cancer. 2015;13:525-30.e1-3.
21. Park J, Cho SY, Jeong SH, Lee SB, Son H, Jeong H. Low testosterone level is an independent risk factor for high-grade prostate cancer detection at biopsy. BJU Int. 2016;118:230-5.
22. Richstone L, Bianco FJ, Shah HH, Kattan MW, Eastham JA, Scardino PT, et al. Radical prostatectomy in men aged >or=70 years: effect of age on upgrading, upstaging, and the accuracy of a preoperative nomogram. BJU Int. 2008;101:541-6.
23. Sun L, Caire AA, Robertson CN, George DJ, Polascik TJ, Maloney KE, et al. Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras. J Urol. 2009;182:2242-8.
24. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360:1310-9. Erratum in: N Engl J Med. 2009;360:1797.
25. Richie JP, Catalona WJ, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. Urology. 1993;42:365-74.
26. Carvalhal GF, Smith DS, Mager DE, Ramos C, Catalona WJ. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4ng./ml. or less. J Urol. 1999;161:835-9.
27. Sung JC, Kabalin JN, Terris MK. Prostate cancer detection, characterization, and clinical outcomes in men aged 70 years and older referred for transrectal ultrasound and prostate biopsies. Urology. 2000;56:295-301.
28. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer. 2015;137:1749-57.
29. Pepe P, Pennisi M. Gleason score stratification according to age at diagnosis in 1028 men. Contemp Oncol (Pozn). 2015;19:471-3.
30. Nardi AC, Reis RB, Zequi Sde C, Nardozza A Jr. Comparison of the epidemiologic features and patterns of initial care for prostate cancer between public and private institutions: a survey by the Brazilian Society of Urology. Int Braz J Urol. 2012;38:155-64.

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ORIGINAL ARTICLE

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Bone scan positivity in non-metastatic, castrate-resistant prostate cancer: external validation study

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ABSTRACT

Introduction: Tables predicting the probability of a positive bone scan in men with non-metastatic, castrate-resistant prostate cancer have recently been reported. We performed an external validation study of these bone scan positivity tables.
Materials and Methods: We performed a retrospective cohort study of patients seen at a tertiary care medical center (1996-2012) to select patients with non-metastatic, castrate-resistant prostate cancer. Abstracted data included demographic, anthropometric, and disease-specific data such as patient race, BMI, PSA kinetics, and primary treatment. Primary outcome was metastasis on bone scan. Multivariable logistic regression was performed using generalized estimating equations to adjust for repeated measures. Risk table performance was assessed using ROC curves.
Results: We identified 6.509 patients with prostate cancer who had received hormonal therapy with a post-hormonal therapy PSA ≥2ng/mL, 363 of whom had non-metastatic, castrate-resistant prostate cancer. Of these, 187 patients (356 bone scans) had calculable PSA kinetics and ≥1 bone scan. Median follow-up after castrate-resistant prostate cancer diagnosis was 32 months (IQR: 19-48). There were 227 (64%) negative and 129 (36%) positive bone scans. On multivariable analysis, higher PSA at castrate-resistant prostate cancer (4.67 vs. 4.4ng/mL, OR=0.57, P=0.02), shorter time from castrate-resistant prostate cancer to scan (7.9 vs. 14.6 months, OR=0.97, P=0.006) and higher PSA at scan (OR=2.91, P <0.0001) were significantly predictive of bone scan positivity. The AUC of the previously published risk tables for predicting scan positivity was 0.72.
Conclusion: Previously published risk tables predicted bone scan positivity in men with non-metastatic, castrate-resistant prostate cancer with reasonable accuracy.

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INTRODUCTION

Non-metastatic castrate resistant prostate cancer (M0 CRPC) carries a large burden of disease. Patients are largely asymptomatic in this disease state, thus, it is an important clinical goal to prevent further progression to metastatic disease. Within 2 years, 46% of M0 CRPC patients develop metastases with 33% representing bony metastases (1, 2). The progression from M0 to metastatic (M1) CRPC is a seminal event affecting patient and provider decision-making (3). While two drugs are approved for M0 CRPC, apalutamide and enzalutamide (4), there are a multitude of options in the treatment of M1 CRPC including abiraterone, sipuleucel-T, and denosumab (5-7), and perhaps

in the future, combination therapies that are not available for M0 CRPC. In addition, given differing outcomes of M0 and M1 CRPC patients, positive imaging has a strong prognostic value. Thus, the separation of M0 CRPC from M1 CRPC remains critically important.

The ability to detect progress is not well understood given the heterogeneity of this disease stage. Thus, the challenge is to identify clinical factors that would appropriately trigger ordering a bone scan in CRPC patients. Prior studies have shown that among men with presumed M0 CRPC, upwards of one-third of patients actually have M1 CRPC when subjected to a metastatic work up (8). Unfortunately, there are studies showing that bone scans may be either over- or underused in this common clinical scenario (9, 10). In order to identify men at high-risk for a positive bone scan, data including PSA levels and kinetics from 312 men were used to develop prediction tables. Frequent PSA levels are affordable and the standard of care making them an attractive trigger. The original study developing these prediction tables was conducted using data from two Veterans Affairs (VA) medical centers (11), and the subsequent validation study was performed in 3 additional VA medical centers involving 281 men (12). In the current climate of scientific rigor, validation and replication are becoming increasingly important. We therefore performed a validation study at a large tertiary academic medical center. Our objective was to generalize the prior studies into a population of non-VA patients.

MATERIALS AND METHODS

Study Population

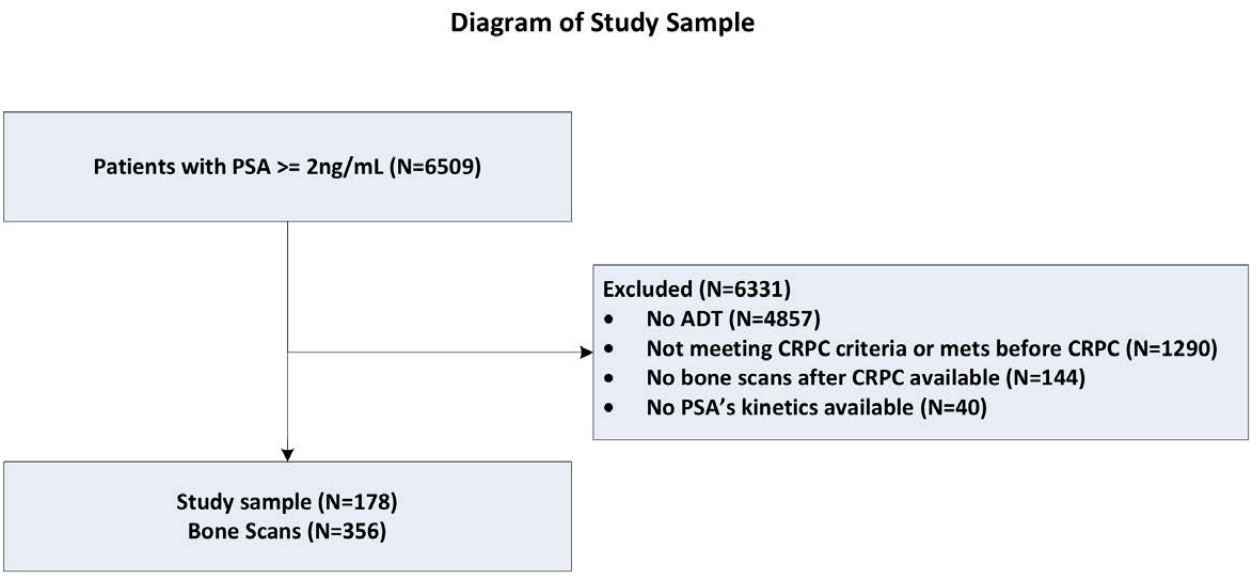
After receiving Institutional Review Board approval, patient records from our institution were reviewed. Based on electronic billing records augmented by a detailed chart review, we identified 6.509 patients with prostate cancer, who had received at least 1 dose of androgen deprivation therapy (ADT), and who had a PSA value ≥2.0ng/mL after the receipt of ADT. Medical records were manually screened to select patients with documented M0 CRPC. Of these 6.509 patients, 4.847 were excluded for not having continuous ADT. Another 1.290 were excluded for not having CRPC or having documented metastatic disease prior to CRPC diagnosis. Thus, 363 patients had documented M0 CRPC as defined by the Prostate Cancer Working Group 2 definition: a 25% or greater rise in PSA and an absolute increase of ≥ 2.0ng/mL from the post-ADT PSA nadir while receiving continuous ADT or after orchiectomy (11). Our final cohort was limited to 187 patients who had at least one bone scan after CRPC diagnosis as well as available PSA kinetics (Figure-1). The final database included information on race, age at the time of bone scans, height, weight, PSA, diagnosis date, primary treatments, clinical and pathological characteristics, PSA values, bone scan results, as well as follow-up. Bone scan results were coded as positive or negative based on the radiology reports and subsequent imaging (if equivocal). Equivocal scans were considered negative unless proven positive by a second imaging modality or biopsy. Patients were followed up to their first positive bone scan. Once a patient was documented as having bony metastasis no further scans were reviewed.

Statistical analysis

PSA doubling time (PSADT) was calculated by the natural log of two divided by the slope of the linear regression of the natural log of the PSA over time in months. PSA's from the time of CRPC diagnosis or two years prior to the scan (whichever was closer to the scan) up until the scan date were included in PSADT calculations. To calculate a PSADT, ≥ 2 PSA's over at least three months were required. If PSADT was declining or at >120 months a PSADT of 120 was assigned for ease of analysis.

Baseline characteristics (at time of CRPC index date) were summarized using median, and first and third quartiles for continuous variables and frequency and percentages for categorical variables. Univariable models were fit with the following variables: age at CRPC index date (years), year of scan, race (black or non-black), biopsy pathological grade group (1-5), primary treatment (radical prostatectomy ± radiation, radiation only, other/unknown), time from ADT to CRPC (mon-

Figure 1 - CONSORT diagram of the study population.



ths), PSA at CRPC index date (ng/mL), time from CRPC to scan (months), PSA at time of scan (ng/mL) and PSADT at the time of scan (months). PSA at the time of scan was log transformed. Age at CRPC and year of scan were centered by their mean value to eliminate multicollinearity. These characteristics were compared between the subsets of negative and positive bone scans. To account for multiple bone scans per patient (repeated measures), P-values were calculated using generalized estimating equations (GEE) using a logit link, autoregressive correlation structure, and type 3 estimation.

Multivariable analyses were also performed using GEE methods including all covariates from the univariable analysis. Pre-scan PSA and PSADT were somewhat correlated (Spearman=-0.11, P-value 0.04), but not collinear and thus both variables were retained in the analysis.

To assess the performance of the Moreira et al. risk table to predict bone scan positivity among men with M0 CRPC in our cohort, PSA levels were divided into four groups (<5, 5- <15, 15- <50, ≥50) and PSADT was divided into four groups (≥ 15, ≥ 9-15, ≥ 3-9, and <3) based on previously identified cut points (11). A calibration curve was performed to show the performance of the risk table. ROC curves were constructed and AUC calculated to assess the predictive accuracy of the Moreira et al. model compared to our cohort.

All statistical analyses were performed using SAS version 9.4 and R version 3.4.1.

RESULTS

Among the 187 patients with PSA kinetic data, 356 bone scans were performed from CRPC diagnosis until the first positive scan. Median age of CRPC diagnosis was 72 years (IQR: 64-79) and median year of diagnosis was 2008 (IQR: 2004-2010) ranging from 1997 to 2012. Median follow-up after CRPC diagnosis was 32 months (IQR: 19-48) (Table-1). Median number of bone scans per patient was 1 (IQR: 1-2). The maximum number of scans for one individual was 12. Half of the subjects (51%) had only one bone scan. A positive scan for metastasis was noted in 73%; of those with metastasis, 69% were diagnosed on their first scan after CRPC diagnosis. Of those without a positive scan, 22% had more than 5 scans. No subjects with a positive scan had more than 5 scans.

Baseline characteristics stratified by positive and negative scan results are shown in Table-2. Patients are repeated in these counts if they had

Table 1 - Baseline Patient Characteristics.

Variables	N=187
Number of Bone Scans, median (Q1, Q3)	1 (1, 2)
Age at CRPC (years), median (Q1, Q3)	72 (64, 79)
Year of CRPC Diagnosis, median (Q1, Q3)	2008 (2004, 2010)
Race, N (%)	
Non-black	135 (72)
Black	52 (28)
Biopsy Gleason Score, N (%)	
2-6	35 (19)
7	43 (23)
8-10	48 (26)
Unknown/No Biopsy	61 (32)
Primary Treatment, N (%)	
None/Unknown/Other	70 (37)
RP ± Radiation	80 (43)
Radiation Alone	37 (20)
Time from ADT to CRPC (months), median (Q1, Q3)	39 (18, 65)
PSA at Diagnosis (ng/mL), median (Q1, Q3)	12.2 (7.0, 25.9)
PSA at CRPC (ng/mL), median (Q1, Q3)	4.6 (2.8, 10.1)
Total Follow-up (months), Median (Q1, Q3)	32 (19, 48)

more than one scan. There were 227 (64%) negative and 129 (36%) positive bone scans. Positive bone scans were associated with tendency to have radical prostatectomy+/-radiation as primary treatment (46% vs. 33%, OR=2.32, P=0.016) and greater pre-scan PSA value (27.3 vs. 7.1, OR=1.97, P <0.0001), compared to negative scans (Table 2 and 3). Younger age (70 vs. 73 years, OR=0.97, P=0.019), and shorter pre-scan PSADT (5.9 vs. 11.3, OR=0.68, P=0.0002) were statistically significantly related to scan positivity. There were no associations between bone scan positivity and year of bone scan, race, biopsy pathological grade group, time from ADT to CRPC, or time from CRPC to scan (all p-values >0.08).

On multivariable analysis, higher PSA at CRPC (4.67 vs. 4.4ng/mL, OR=0.57, P=0.02), shorter time from CRPC to scan (7.9 vs. 14.6 months, OR=0.97, P=0.006), and higher pre-scan PSA (OR=2.91, P <0.0001) were significantly predictive of bone scan positivity.

In the analysis by PSA groups (Chi-square), the scan positivity was 8.8%, 40.4%, 35.4%, and 63.8% for men with PSA <5, 5- <15, 15- <50, ≥ 50ng/mL, respectively (Figure-2A, P<0.0001). Men with PSADT ≥ 15, ≥ 9-15, ≥ 3-9, and <3months had scan positivity of 23.8%, 28.6%, 42.6%, and 65.8%, respectively (Figure-2B, P <0.0001). The AUC of the Moreira et al. table in predicting rates of positive scan was 0.72 (Figure-3). A calibration curve de-

Table 2 - Baseline Patient Characteristics.

Variables	Negative Bone Scan N=227	Positive Bone Scan N=129	P*
Age at CRPC (years), median (Q1, Q3)	73 (67, 79)	70 (63, 77)	0.019
Year of Scan, median (Q1, Q3)	2009 (2007, 2011)	2009 (2006, 2010)	0.768
Race, N (%)			
Non-black	158 (70)	94 (73)	0.655
Black	69 (30)	35 (27)	
Biopsy Gleason Score, N (%)			0.68
2-6	51 (22)	24 (19)	
7	55 (24)	28 (22)	
8-10	53 (23)	37 (29)	
Unknown/No Biopsy	68 (30)	40 (31)	
Primary Treatment, N (%)			**0.016**
None/Unknown/Other	118 (52)	41 (32)	
RP ± Radiation	74 (33)	59 (46)	
Radiation Alone	35 (15)	29 (22)	
Time from ADT to CRPC (months), median (Q1, Q3)	41 (28, 65)	34 (17, 60)	0.159
PSA at CRPC (ng/mL), median (Q1, Q3) ¥	4.4 (2.8, 9.13)	4.67 (2.79, 10.88)	0.082
Time from CRPC to scan (months), median (Q1, Q3)	14.59 (5.05, 29.27)	7.89 (2.92, 21.35)	0.766
Pre-scan PSA (ng/mL), median (Q1,Q3) ¥	7.1 (2.9, 19.86)	27.25 (9,79.6)	<0.0001
Pre-scan PSADT (ng/mL), median (Q1, Q3) ¥	11.34 (6.00, 44.66)	5.91 (3.41, 13.42)	0.0002

¥ = Log-transformed variable was used in this analysis

monstrated good agreement between predicted and actual probability of a positive scan, except if the estimated probability of a positive scan was <40%, when the model mostly underestimated the probability of a positive result (Tables 4 and 5, Figure-4).

DISCUSSION

Approximately 90% of men with CRPC will develop bone metastases and the burden of disease correlates directly with survival (13). While the AUA, EAU, and NCCN guidelines provide clear recommendations for initial screening with a bone scan at the time of diagnosis in high-risk men, they do not provide specific recommendations for metastatic screening of asymptomatic CRPC patients (14-16). The algorithm we sought to validate in this study takes advantage of PSA and PSADT to create a prediction tool to predict the risk of a positive bone scan among men with M0 CRPC and fill a gap in existing guidelines. Prediction tools tend to outperform human experts (17), and the algorithm validated in this study serves to augment the existing guidelines and avoid unnecessary bone scans, while still identifying metastatic disease.

Table 3 - Predictors of Bone Scan Positivity.

Variables	Univariate Results		Multivariate Results	
	OR (95% CI)	P	OR (95% CI)	P
Age at CRPC (years), median (Q1, Q3)	0.97 (0.94-0.99)	0.019	0.99 (0.96-1.03)	0.697
Year of Scan, median (Q1, Q3)	0.99 (0.92-1.06)	0.768	1.06 (0.97-1.16)	0.204
Race, N (%)		**0.655**		0.738
Non-black	ref		ref	
Black	0.87 (0.47-1.6)		1.13 (0.54-2.38)	
Biopsy Gleason Score, N (%)		0.68		0.632
2-6	ref		ref	
7	1.04 (0.46-2.34)		1.25 (0.50-3.1)	
8-10	1.54 (0.69-3.46)		1.60 (0.66-3.92)	
Unknown/No Biopsy	1.18 (0.55-2.54)		1.69 (0.72-3.97)	
Primary Treatment, N (%)		0.016		0.12
None/Unknown/Other	ref		ref	
Radiation Alone	2.24 (1.15, 4.35)		1.85 (0.78-4.42)	
RP ± Radiation	2.32 (1.25, 4.32)		2.37 (1.02-5.49)	
Time from ADT to CRPC (months), median (Q1, Q3)	0.99 (0.99-1.00)	0.159	1.00 (0.99-1.01)	0.729
PSA at CRPC (ng/mL), median (Q1, Q3) ¥	1.26 (0.98-1.61)	0.082	0.57 (0.37-0.87)	0.016
Time from CRPC to scan (months), median (Q1, Q3)	1.00 (0.98-1.01)	0.766	0.97 (0.95-0.99)	0.006
Pre-scan PSA (ng/mL), median (Q1,Q3) ¥	1.97 (1.65-2.35)	<0.0001	2.91 (2.17-3.92)	<0.0001
Pre-scan PSADT (ng/mL), median (Q1, Q3) ¥	0.68 (0.57-0.82)	0.0002	1.12 (0.87-1.46)	0.386

¥ = Log-transformed variable was used in this analysis

The AUC is a measure of the accuracy of a test. Our goal was to test how accurately the Moreira et al. tables can distinguish between the group of men who will have a positive or negative bone scan. An AUC of 0.72 represents a good test for clinical applications. Our study validates this tool in a cohort with both a large proportion (28%) of African Americans and further expands its use beyond the VA to the general population.

Many of the large prostate cancer trials are predominantly comprised of European men or men of European descent. The development and validation of the Moreira et al. tables included a large portion of African American men. SEER data has demonstrated that African American men have a 64% higher incidence of prostate cancer than white men (18). They also tend to present with higher grade and stage tumors, leading to a 2.4-fold increase in prostate cancer mortality when compared to white men (19). Prior to published guidelines in the mid-90s, African American men were less likely to undergo appropriate imaging, but this difference was resolved with more contemporary studies (20). Within this cohort, the median baseline PSA was higher (<0.001), and the PSADT was shorter (p <0.01) for African Americans with

Figure 2 - Bone scan positivity by PSA (A) and by PSA doubling time (B).

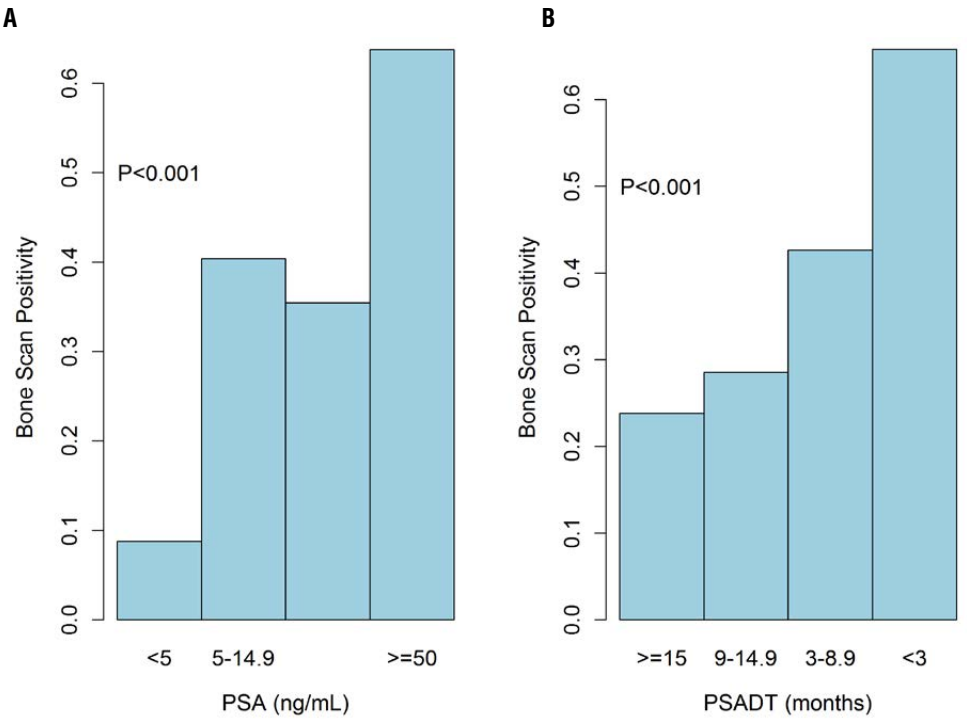


Figure 3 - Receiver-Operator Characteristics Curve of the Moreira Tables Predicting Bone Scan Positivity.

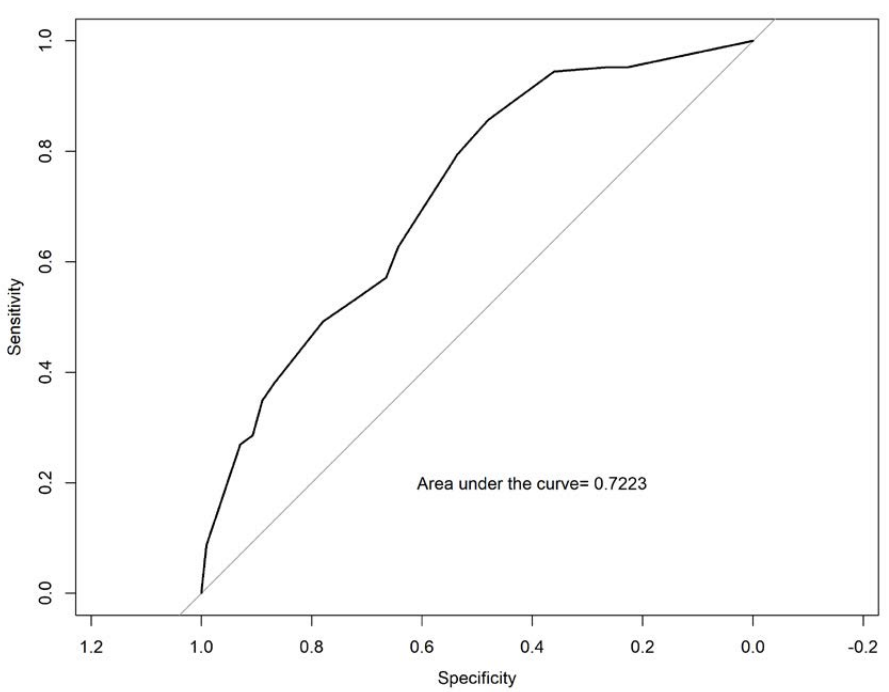


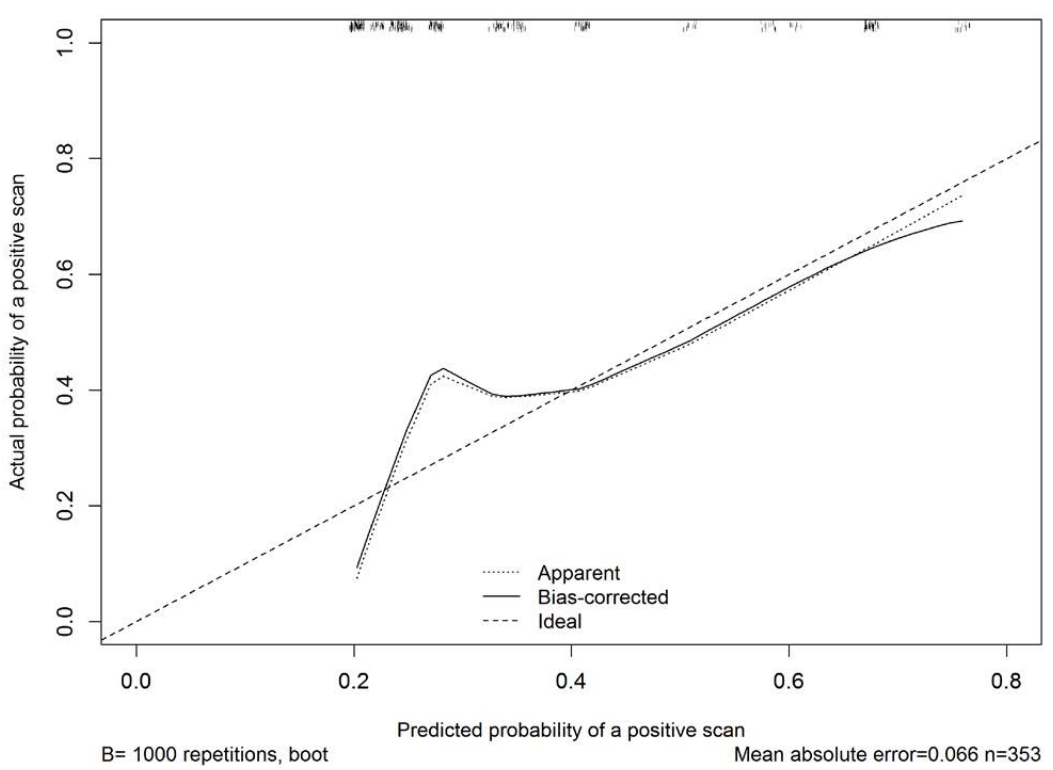
Table 4 - Moreira et al. (11) Predicted risk of positive scan by PSA and PSADT groups.

PSADT (months)	PSA (ng/mL)			
	<5	5-14.9	15-49.9	≥ 50
≥ 15	6 (4-8)	11 (9-14)	22 (18-28)	47(40-54)
9-14.9	6 (4-10)	12 (10-14)	24 (22-26)	49 (46-52)
3-8.9	8 (5-14)	16 (13-18)	30 (27-33)	57 (53-60)
<3	12 (8-19)	22 (19-25)	40 (37-42)	67 (64-69)

Table 5 - Predicted risk of positive scan by PSA and PSADT groups.

PSADT (months)	PSA (ng/mL)			
	<5	5-14.9	15-49.9	≥ 50
≥ 15	10 (6/58)	29 (11/38)	28 (5/18)	67 (8/12)
9-14.9	0 (0/9)	38 (8/21)	28 (5/18)	29 (2/7)
3-8.9	5 (1/22)	47 (20/43)	41 (14/34)	62 (23/37)
<3	50 (1/2)	58 (7/12)	44 (4/9)	85 (11/13)

Figure 4 - Calibration curve demonstrating general agreement between predicted and actual probability of a positive scan.



prostate cancer compared to white men (21). There is evidence that even after adjusting for differences in social determinants of health, a higher mortality rate from prostate cancer still persists for African American compared to white men (22). North Carolina's population is 21% African American; the incidence of prostate cancer in this population is 216.5 per 100.000 (disparity ratio of 1.7) and the mortality rate is 44.2 per 100.000 (disparity ratio of 2.5) (23). Valid prediction tools for the African American population are thus understudied but essential.

In addition to including a large portion of African Americans, this study population moves beyond the VA and into the broader community. The patient population from the VA have contributed greatly to medicine, and there are several seminal manuscripts in urology, particularly prostate cancer, that derive from this cohort (24). Prostate cancer treatment is similar between the VA and general community (25). However, VA patients are a unique subset of the American public, and have a distinct demographic distribution. VA patients tend to be older, sicker, and of lower socioeconomic status than the US population (26). Patients at the VA are diagnosed with commonly occurring cancers at earlier stages, relative to the general population (25). Prostate cancer accounts for roughly 33% of cancer diagnoses among men within the VA, and only 25% in the general population (26.). Validation in a tertiary hospital makes the results more generalizable.

Our results showed that a positive scan was more likely to be associated with a history of radical prostatectomy. This would suggest that in the setting of extirpative surgery, a rising PSA is more likely to come from a metastasis than a local recurrence, and this has been seen before, even in the setting of node positive disease (27, 28).

This study has several limitations. It is a retrospective study in a single institution, and as such these data subject to secular trends, practice pattern variation, and/or care differences that may limit the generalizability of its findings. Furthermore, this institution is a tertiary medical center, and thus these findings (particularly the severity of disease in this population) may not be truly representative of the broader prostate cancer community. Also, it is possible that with a larger study, other variables, such as Gleason score, may correlate with positive imaging that could further improve risk stratification. Nonetheless, the facts that these tables are accurate in both a VA setting and a tertiary care facility gives some credence that these can be widely applied, though ideally validation in the community would be needed. While a 10% duplicate data entry system and rigorous data quality checks were used throughout data abstraction and analysis, these data may also be subject to information or miscoding bias, as with any retrospective analysis. Finally, while they are clinically useful, the accuracy of the tables may not be ideal. As such, future research should focus on additional biomarkers of metastases to further aid in risk stratification for this important group of prostate cancer patients.

CONCLUSIONS

In conclusion, among men with M0 CRPC seen at a tertiary care academic medical center, the Moreira et al. risk tables predicted bone scan positivity with reasonable accuracy and significant improvement over PSA and PSA kinetics alone. The tables have now been externally validated using multiple datasets and appear to be generalizable to the larger medical community.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Smith MR, Cook R, Lee KA, Nelson JB. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer. 2011;117:2077-85.

2. Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol. 2005;23:2918-25.
3. Crawford ED, Stone NN, Yu EY, Koo PJ, Freedland SJ, Slovin SF, et al. Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group. Challenges and recommendations for early identification of metastatic disease in prostate cancer. Urology. 2014;83:664-9.
4. [No Authors]. FDA Approves Apalutamide for Prostate Cancer - National Cancer Institute. 2018. Available at. <https://www.cancer.gov/news-events/cancer-currents-blog/2018/apalutamide-fda-nonmetastatic-prostate>.
5. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138-48. Erratum in: N Engl J Med. 2013;368:584.
6. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363:411-22.
7. Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet. 2012;379:39-46.
8. Yu EY, Miller K, Nelson J, Gleave M, Fizazi K, Moul JW, et al. Detection of previously unidentified metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic, castration resistant prostate cancer. J Urol. 2012;188:103-9.
9. Falchook AD, Salloum RG, Hendrix LH, Chen RC. Use of bone scan during initial prostate cancer workup, downstream procedures, and associated Medicare costs. Int J Radiat Oncol Biol Phys. 2014;89:243-8.
10. Makarov DV, Desai RA, Yu JB, Sharma R, Abraham N, Albertsen PC, et al. The population level prevalence and correlates of appropriate and inappropriate imaging to stage incident prostate cancer in the medicare population. J Urol. 2012;187:97-102.
11. Moreira DM, Howard LE, Sourbeer KN, Amarasekara HS, Chow LC, Cockrell DC, et al. Predicting bone scan positivity in non-metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2015;18:333-7.
12. Freedland SJ, Howard LE, Hanyok BT, Kadiyala VK, Kuang JY, Whitney CA, et al. Validation of a bone scan positivity risk table in non-metastatic castration-resistant prostate cancer. BJU Int. 2016;118:570-7.
13. Cooper CR, Chay CH, Gendernalik JD, Lee HL, Bhatia J, Taichman RS, et al. Stromal factors involved in prostate carcinoma metastasis to bone. Cancer. 2003;97(3 Suppl):739-47.
14. Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, et al. Prostate Cancer, Version 1.2016. J Natl Compr Canc Netw. 2016;14:19-30.
15. Lowrance WT, Roth BJ, Kirkby E, Murad MH, Cookson MS. Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2015. J Urol. 2016;195:1444-52.
16. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467-79.
17. Ross PL, Gerigk C, Gonen M, Yossepowitch O, Cagiannos I, Sogani PC, et al. Comparisons of nomograms and urologists' predictions in prostate cancer. Semin Urol Oncol. 2002;20:82-8.
18. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30.
19. Moul JW. Targeted screening for prostate cancer in African-American men. Prostate Cancer Prostatic Dis. 2000;3:248-55.
20. Abraham N, Wan F, Montagnet C, Wong YN, Armstrong K. Decrease in racial disparities in the staging evaluation for prostate cancer after publication of staging guidelines. J Urol. 2007;178:82-7.
21. Armstrong AJ, Higano CS, Cooperberg MR, Ahaghotu C, Tutrone RF, Belkoff LH, et al. Characteristics and anticancer interventions (ACIs) in African American (AA) and Caucasian (CAU) patients (pts) treated with sipuleucel-T (sip-T): Real-world experience from the PROCEED registry. J Clin Oncol. 2016; 34:5025.
22. Robbins AS, Whittemore AS, Thom DH. Differences in socioeconomic status and survival among white and black men with prostate cancer. Am J Epidemiol. 2000;151:409-16.
23. [No Authors] NC SCHS: Statistics and Reports: Cancer Incidence in North Carolina 2014. Available at. <https://schs.dph.ncdhhs.gov/data/cancer/incidence/2014.htm>.
24. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol. 1974;111:58-64.
25. Keating NL, Landrum MB, Lamont EB, Bozeman SR, Krasnow SH, Shulman LN, et al. Quality of care for older patients with cancer in the Veterans Health Administration versus the private sector: a cohort study. Ann Intern Med. 2011;154:727-36.

26. Agha Z, Lofgren RP, VanRuiswyk JV, Layde PM. Are patients at Veterans Affairs medical centers sicker? A comparative analysis of health status and medical resource use. Arch Intern Med. 2000;160:3252-7.
27. Nini A, Gandaglia G, Fossati N, Suardi N, Cucchiara V, Dell'Oglio P, et al. Patterns of Clinical Recurrence of Node-positive Prostate Cancer and Impact on Long-term Survival. Eur Urol. 2015;68:777-84.
28. Whitney CA, Howard LE, Amling CL, Aronson WJ, Cooperberg MR, Kane CJ, et al. Race does not predict the development of metastases in men with nonmetastatic castration-resistant prostate cancer. Cancer. 2016;122:3848-55.

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ORIGINAL ARTICLE

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Validation of the international consultation on incontinence modular questionnaire – female lower urinary tract symptoms (iciq-fluts) into brazilian portuguese

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ABSTRACT

Purpose: To translate, adapt and validate the International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms ICIQ-FLUTS for the Brazilian female population.

Materials and Methods: A translation of the questionnaire into Brazilian Portuguese was made followed by an adaptation for better understanding by native speakers. After that, the ICIQ-FLUTS was answered by eighty volunteers (n=80) twice (for interviewers 1 and 2) with an interval of 30 minutes between them. Furthermore, after 15 days from the evaluation, the participants answered the ICIQ-FLUTS again in order to verify the questionnaire stability over time. The questionnaires Utian Quality Of Life (UQOL) and International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF), which are validated in Brazil were also applied to perform the validation.

Results: The result of the Cronbach α coefficient of the instrument presented a value of 0.832. The values for test-retest were 0.907 (inter-observer) and 0.901 (intra-observer). The correlation between ICIQ-FLUTS (score I - domain of urinary incontinence) with the ICIQ-SF (final score) was strong and positive (r=0.836, p=0.000). In addition, the ICIQ-FLUTS showed moderate and negative correlation with the total score of UQOL (r=-0.691, p=0.017).

Conclusion: The Portuguese version of the ICIQ-FLUTS questionnaire showed strong correlation to ICIQ-SF questionnaire and satisfactory values to test-retest and internal consistency.

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INTRODUCTION

Lower urinary tract symptoms (LUTS) are defined as changes in the storage, voiding and/or post-voiding phase of the urination process, for example, overactive bladder syndrome, nocturia, urinary incontinence (UI), among others (1). LUTS is a clinical condition with a high prevalence in the general population, exceeds 60% in Europe and North America (2, 3), similar results to those found in a Brazilian study (59% in women aged ≥40 years) (4).

The presence of the symptoms mentioned above can negatively affect the women's quality

of life, therefore, LUTS is considered a serious and relevant health problem for women, and its evaluation is important for further treatment (4, 5).

The International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) is a tool which allows to evaluate and quantify LUTS and their impact on quality of life (6). The instrument is derived from the Bristol Female Lower Urinary Tract Symptoms Questionnaire originally developed in English. The final version removed issues in relation to sexuality and included a scoring system divided into three domains: filling, voiding and incontinence (7).

There are validated questionnaires in Brazil used to evaluate UI (8-10), however, the involuntary loss of urine is just one of several types of LUTS. The lack of instruments which evaluate LUTS may difficult its investigation, treatment, as well as the knowledge about the impact of the disease on the quality of life.

Many studies including randomized and controlled clinical trials apply validated questionnaires to evaluate the outcomes of researches. The ICIQ-FLUTS approaches a wide diversity of urinary symptoms presenting level of evidence "A", thus, highly recommended by the International Consultation on Incontinence (ICI). Furthermore, it is brief and presents a good acceptation in clinical practice (11).

Due to the high prevalence of LUTS in women, it is evident that there is a need to create new tools for evaluating urinary symptoms in a broader way. The translation and validation for other languages provide further comparison between studies. In relation to this, the objective of this study was to translate, adapt and validate the ICIQ-FLUTS for the Brazilian female population.

MATERIALS AND METHODS

A prospective validation study was realized in Brazil. This study aims the translation, adaptation and validation of the International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms (ICIQ-FLUTS). The ICIQ group authorized the validation of the ICIQ-FLUTS questionnaire for Brazil.

Participants

A total of 240 users of the urology and gynecology services in Maternidade Escola Januário Cicco of Federal University of Rio Grande do Norte (MEJC/UFRN) participated in the study. A subjects-to-variables ratio of 10:1 was considered as an adequate sample size. Therefore, a minimum of 240 women was required (12).

The inclusion criteria were: (a) be over 18 years of age, (b) with or without LUTS, and (c) not be pregnant or lactating. Those who: (a) gave up participating in the survey or withdrew their consent, or (b) presented an cognitive inability to respond to the questions were excluded from the research.

Instruments

The ICIQ-FLUTS consists of 12 questions related to LUTS divided into three areas: filling (4 questions), voiding (3 questions), and incontinence (5 questions). The answers are based on experiences with LUTS in the previous four weeks. The score is calculated by domain and it ranges from zero to ten in each question (11).

Initially, all volunteers responded a form elaborated for this study with identification and sociodemographic data in addition to questions in relation to clinical aspects (use of medication, associated diseases, practice of physical activity, obstetrics and gynecology history).

The translation and adaptation of the ICIQ-FLUTS were carried out following standard guidelines (11).

1 - Initial translation of the questionnaire into Portuguese was undertaken by two bilingual native speakers, independently. Synthesis of the translation by the two translators (V1).
2 - Back translation into English by two native English speakers.
3 - Review of the back translations by the ICIQ group and adjustment.
4 - Spelling and semantic corrections for the creation of the second version in Portuguese (V2).

To verify the validity of the questionnaire (12), the V2 of the translated questionnaire was presented to a group of 5 patients who met the in-

clusion criteria of the study, as well as by a group of professionals which included physiotherapists, urologists and gynecologists. The observations made at this stage were performed, which resulted in small textual changes in the questions for better understanding.

Eighty (n=80) volunteers were randomly selected within the sample to participate in the inter-rater reliability analysis. The participants answered the ICIQ-FLUTS questionnaire for interviewer 1 and interviewer 2 after 30 minutes of finalizing the first evaluation. The order of the evaluators was always the same.

The stability of the questionnaire over time was verified with other group of eighty volunteers (n=80). The participants answered the questionnaire twice with an interval of 15 days between the evaluations. It is expected that LUTS will not undergo a significant change within its clinical condition during this period (12).

The validation was performed applying two questionnaires which had already been translated and validated in Brazil. The Utian Quality Of Life (UQOL) was validated for the Brazilian population by Lisboa et al. (13). Although the questions are not specific for the climacteric period, it is a questionnaire designed to quantify the quality of life during this phase of life. In total, there are 23 questions distributed in four domains on quality of life: occupational, health, sexual and emotional. The higher the score, the better the quality of life.

The other used questionnaire was the International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF). This questionnaire is a simple, brief and self-applied questionnaire, which assesses the impact of UI in quality of life and qualifies the urinary loss and it was translated and validated to Portuguese Language by Tamanini et al. (8). It consists of four questions that evaluate the frequency, severity and the impact of UI, in addition to a set of eight self-diagnosis items that allows to evaluate the causes or situations of UI experienced by the patients. The total score ranges from zero to twenty-one points and is divided into: no impact (0 point), light impact (1 to 3 points), moderate (4 to 6 points), severe (7 to 9 points) and very severe (10 or more points).

Statistical analysis

Descriptive statistical was performed to present the information about sociodemographic and clinical aspects. The internal consistency assessment was performed using the Cronbach's alpha coefficient statistical test. The intra and inter-rater reliability were verified using the Intraclass Correlation Coefficient (ICC). The correlations were performed using the Pearson Correlation Test. The Statistical Package for Social Sciences version 20.0 program for Windows was used.

Ethical issues

All the volunteers signed the Consent Term. The research was approved by the Ethics and Research Committee (number 1.846.197/2016) of the Federal University of Rio Grande do Norte.

RESULTS

A total of 240 patients were interviewed, six of whom were excluded as they did not complete the questionnaire responses. 234 patients were included in the data analysis, with mean age of 50.96 years (±11.22) (CI: 49.28-52.65). The majority of the volunteers presented 1-2 Brazilian basic salary (45.4%), studied up to 10 years of schooling (30.5%) and had status marital married (59.7%).

The mean number of pregnancies was 3.18±0.15 (CI: 2.88-3.49), vaginal delivery was 2.09±0.14 (CI: 1.81 - 2.38) and cesarean section was 0.55±0.05 (CI: 0.44-0.67). According to hormonal status, 38.5% of the sample was in the reproductive phase, 8.3% in the menopausal transition period and 53.2% in the menopausal period. The time of menopause was 10.03±4.26 years. Table-1 shows the characteristics of the volunteers.

The result of the Cronbach α coefficient of the instrument presented a value of 0.832. The inter-rater and intra-rater reliability are presented in Table-2.

The correlation between ICIQ-FLUTS (score I - domain of urinary incontinence) with the ICIQ--SF (final score) was strong and positive (r=0.836,

p=0.000). The ICIQ-FLUTS also showed moderate and negative correlation with the total score of UQOL (r=-0.691, p=0.017). The mean scores and correlation between the questionnaires are shown in Table-3.

DISCUSSION

Throughout women's life, the onset of different types of LUTS is frequent though most evaluations or therapeutic approaches highlight only urinary incontinence among its symptoms. The ICIQ-FLUTS is a questionnaire which investigates female lower urinary tract symptoms by recording the degree of discomfort from the presence of this symptom. This questionnaire was chosen to be translated, adapted and validated for Portuguese because it is brief, applied over a few minutes, has a simple scoring method and identifies other urinary symptoms such as nocturia, dysuria and urgency. Moreover, it has already been translated for other languages such as Tamil (14), Greek (15), Chinese (16), Dutch, Danish, French, German, Korean, Norwegian and Swedish (11). The ICIQ-FLUTS validation process for the languages described above used ICIQ-SF and all results showed great reliability when related to the questionnaires.

The internal consistency of the ICIQ--FLUTS measured by the Cronbach α Coefficient was considered satisfactory. The ICIQ group (11) recommends 0.70 as the minimum acceptable value. In a recent validation study of the instrument for Tamil (14), this value was 0.80. Thus, we can demonstrate that the instrument has a good degree of correlation between its items.

Table 1 - Characteristics of the volunteers (n=234).

Variables	Number	Frequency (%)
Educational level		
No study	49	21.5
Up to 4 years	40	17.0
5-8 years	24	10.5
9-12 years	74	31.5
Above 13 years	47	20.5
Number of pregnancies		
Nulliparous	16	6.84
1 pregnancy	101	43.16
Above 1 pregnancy	117	50.00
Types of delivery		
Vaginal	170	72.65
Cesarean section	64	27.35
Hormonal Status		
Reproductive phase	90	38.50
Transition	19	8.12
Menopausal period	125	53.38
Menopause (n=125)		
Natural	78	62.50
Surgical	47	37.50

Table 2 - Intra and inter-rater reliability analysis of the ICIQ-FLUTS.

	Intra-rater reliability*	Inter-rater reliability*	Cronbach α coefficient
Question 2[a]	0.932	0.887	0.80
Question 2b	0.871	0.884	0.81
Question 3[a]	0.894	0.921	0.87
Question 2b	0.868	0.923	0.85
Question 4[a]	0.913	0.852	0.78
Question 4b	0.891	0.848	0.80
Question 5[a]	0.901	0.885	0.91
Question 5b	0.848	0.865	0.78
Question 6[a]	0.873	0.994	0.82
Question 6b	0.874	0.986	0.81
Question 7[a]	0.945	0.858	0.87
Question 7b	0.901	0.871	0.89
Question 8[a]	0.932	0.931	0.79
Question 8b	0.912	0.945	0.81
Question 9[a]	0.982	0.923	0.82
Question 9b	0.925	0.932	0.79
Question 10[a]	0.973	0.845	0.90
Question 10b	0.895	0.861	0.89
Question 11[a]	0.864	0.982	0.76
Question 11b	0.842	0.985	0.78
Question 12[a]	0.939	0.896	0.83
Question 12b	0.892	0.921	0.85
Question 13[a]	0.896	0.873	0.88
Question 13b	0.874	0.901	0.88

ICIQ-FLUTS = International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms; **ICC** = Intraclass Correlation Coefficient

The stability of the questionnaire was analyzed through the test-retest. The results demonstrate that the ICIQ-FLUTS has remained sensitive in measuring of LUTS over time. The interval of 15 days was chosen considering that the urinary symptoms should not undergo clinical changes (in the absence of treatment) in this time. Although, it is also expected that the participants do not remember the answers of the first evaluation. The values obtained in the Intraclass Correlation Coefficient test were good.

There was strong and positive correlation between ICIQ-FLUTS and ICIQ-SF. This result demonstrates that the ICIQ-FLUTS is reliably and satisfactorily evaluate UI. It is important to inform that ICIQ-SF is a questionnaire well-known for the scientific and clinical application of only urinary losses (17). Thus, ICIQ-FLUTS seems to be more complete in the wider investigation of other LUTS, since assesses effort and urgency UI, unlike other questionnaires that evaluate separately and focus only on UI.

The correlation between UQOL and ICIQ--FLUTS was moderate in the evaluation of the final score and domains. Perhaps some volunteers do not consider LUTS as a disease that affects their quality of life in various spheres of financial, social and personal aspects. In addition, some

Table 3 - Mean final scores and correlation of the questionnaires ICIQ-FLUTS with ICIQ-SF and UQOL.

	Mean (SD)	CI	Correlation (r)
ICIQ-FLUTS			
ScoreF	11.93 (±0.91)	10.12 - 13.74	-
ScoreV	3.31 (±0.53)	2.25 - 4.36	-
Score I	17.03 (±1.24)	14.57 - 19.49	-
ICIQ-SF	9.13 (±0.57)	7.99 - 10.27	0.83
UQOL			
Occupational	27.56 (±0.31)	19.62 - 20.59	-0.61
Health	20.11 (±0.24)	19.44 - 22.44	-0.74
Emotional	18.85 (±0.27)	18.30 - 19.40	-0.71
Sexual	9.52 (±0.17)	9.17 - 9.87	-0.67
Total	**75.98 (±0.62)**	**74.75 - 77.22**	**-0.69**

I**CIQ-FLUTS** = International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms; **UQOL** = Utian Quality of Life; ICIQ-SF = International Consultation on Incontinence Questionnaire - Short Form; **SD** = standard deviation; **CI** = confidence interval

women believe that involuntary loss of urine is a natural aging process (18).

A limitation of this study was the need to read the questionnaire for a part of the sample (21.5%) that were illiterate. The users from the public health system in Brazil often have a low education level or are illiterate. Other study about validation of questionnaire corroborate this information (19, 20). The questionnaires by ICIQ group are self-administered.

More studies should be carried out to demonstrate the responsiveness of the questionnaire. It means to verify the sensitivity of the questionnaire before and after specific treatment for LUTS. However, the authors hope that the ICIQ-FLUTS can already be used in clinical and scientific research as part of screening for LUTS and monitoring its evolution.

CONCLUSIONS

The Portuguese version of the ICIQ-FLUTS questionnaire showed strong correlation to ICIQ--SF questionnaire and satisfactory values to test--retest and internal consistency. Therefore, it is an important tool to detect LUTS among Brazilian female population.

ABBREVIATIONS

LUTS = Lower Urinary Tract Symptoms
ICIQ-FLUTS = International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms
UI = Urinary Incontinence
MEJC/UFRN = Maternidade Escola Januário Cicco of Federal University of Rio Grande do Norte
UQOL = Utian Quality Of Life
ICIQ-SF = International Consultation on Incontinence Questionnaire - Short Form
ICC = Intraclass Correlation Coefficient
CI = Confidence Interval

CONFLICT OF INTEREST

None declared.

REFERENCES

1. 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.

2. Coyne KS, Sexton CC, Thompson CL, Milsom I, Irwin D, Kopp ZS, et al. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. BJU Int. 2009;104:352-60.
3. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006;50:1306-14.
4. Soler R, Gomes CM, Averbeck MA, Koyama M. The prevalence of lower urinary tract symptoms (LUTS) in Brazil: Results from the epidemiology of LUTS (Brazil LUTS) study. Neurourol Urodyn. 2018;37:1356-64.
5. Bilgic D, Beji NK. Lower urinary tract symptoms in women and quality of life. International Journal of Urological Nursing. 2010;4:97-105.
6. Jackson S, Donovan J, Brookes S, Eckford S, Swithinbank L, Abrams P. The Bristol Female Lower Urinary Tract Symptoms questionnaire: development and psychometric testing. Br J Urol. 1996;77:805-12.
7. Brookes ST, Donovan JL, Wright M, Jackson S, Abrams P. A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: data from a randomized controlled trial of surgery for women with stress incontinence. Am J Obstet Gynecol. 2004;191:73-82.
8. Tamanini JT, Dambros M, D'Ancona CA, Palma PC, Rodrigues Netto N Jr. Validation of the "International Consultation on Incontinence Questionnaire - Short Form" (ICIQ-SF) for Portuguese. Rev Saude Publica. 2004;38:438-44.
9. Tamanini JT, D'Ancona CA, Botega NJ, Rodrigues Netto N Jr. Validation of the Portuguese version of the King's Health Questionnaire for urinary incontinent women. Rev Saude Publica. 2003;37:203-11.
10. Pereira VS, Santos JY, Correia GN, Driusso P. [Translation and validation into Portuguese of a questionnaire to evaluate the severity of urinary incontinence]. Rev Bras Ginecol Obstet. 2011;33:182-7.
11. Bristol Urological Institute,Internacional Consultation on Incontinence Modular Questionnaire (ICIQ). Available at. <http://iciq.net>. Acessed 15 March 2018.
12. Bryant FB, Yarnold PR. Principal-components analysis and exploratory and confirmatory factor analysis. In: Grimm LG, Yarnold PR, editors. Reading and understanding multivariate statistics. Washington DC: American Psychological Association. 1995:99-136.
13. Lisboa LL, Utian W, da Fonseca Filho GG, de Azevedo GD. Translation, adaptation and validation of the Brazilian version of the Utian Quality of Life for evaluation of quality of life in the climacteric. Rev Bras Ginecol Obstet. 2015;37:520-5.
14. Ekanayake CD, Pathmeswaran A, Nishad AAN, Samaranayake KU, Wijesinghe PS. Translation and validation of ICIQ-FLUTS for Tamil-speaking women. Int Urogynecol J. 2017;28:1875-81.
15. Athanasiou S, Grigoriadis T, Kyriakidou N, Giannoulis G, Antsaklis A. The validation of international consultation on incontinence questionnaires in the Greek language. Neurourol Urodyn. 2012;31:1141-4. Erratum in: Neurourol Urodyn. 2012;31:1310.
16. Huang L, Zhang SW, Wu SL, Ma L, Deng XH. The Chinese version of ICIQ: a useful tool in clinical practice and research on urinary incontinence. Neurourol Urodyn. 2008;27:522-4.
17. Abrams P, Andersson KE, Birder L, Brubaker L, Cardozo L, Chapple C, et al. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn. 2010;29:213-40.
18. Shah D, Badlani G. Treatment of overactive bladder and incontinence in the elderly. Rev Urol. 2002;4 Suppl 4:S38-43.
19. Moraes RP, Silva JLD, Calado AA, Cavalcanti GA. Validation of the urgency questionnaire in Portuguese: A new instrument to assess overactive bladder syndrome. Int Braz J Urol. 2018;44:338-347.
20. Pereira SB, Thiel Rdo R, Riccetto C, Silva JM, Pereira LC, Herrmann V, et al. Validation of the International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB) for Portuguese. Rev Bras Ginecol Obstet. 2010;32:273-8.

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ORIGINAL ARTICLE

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Acute prostatitis after prostate biopsy under ciprofloxacin prophylaxis with or without ornidazole and pre-biopsy enema: analysis of 3.479 prostate biopsy cases

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ABSTRACT

Objectives: To investigate the characteristics of cases of NIH category I acute prostatitis developed after transrectal prostate biopsy and clarifiy the risk factors and preventive factors.
Materials and Methods: We retrospectively reviewed the medical records of 3.479 cases of transrectal ultrasound-guided needle biopsies performed with different prophylactic antibiotherapy regimens at two different institutions between January 2011 and February 2016. The patients of Group I have received ciprofloxacin (n=1.523, 500mg twice daily) and the patients of Group II have received ciprofloxacin plus ornidazole (n=1.956, 500mg twice daily) and cleansing enema combination as prophylactic antibiotherapy. The incidence, clinical features and other related microbiological and clinical data, were evaluated.
Results: Mean age was 62.38±7.30 (47-75), and the mean prostate volume was 43.17±15.20 (21-100) mL. Of the 3.479 patients, 39 (1.1%) developed acute prostatitis after the prostate biopsy procedure. Of the 39 cases of acute prostatitis, 28/3.042 occurred after the first biopsy and 11/437 occurred after repeat biopsy (p=0.038). In Group I, 22 of 1.523 (1.4%) patients developed acute prostatitis. In Group II, 17 of 1.959 (0.8%) patients developed acute prostatitis. There was no statistical difference between the two groups according to acute prostatitis rates (X2=2.56, P=0.11). Further, hypertension or DM were not related to the development of acute prostatitis (P=0.76, X2=0.096 and P=0.83, X2=0.046, respectively).
Conclusions: Repeat biopsy seems to increase the risk of acute prostatitis, while the use of antibiotics effective for anaerobic pathogens seems not to be essential yet.

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INTRODUCTION

Transrectal ultrasound-guided needle biopsy (TRUS-Bx) is generally accepted as a standard procedure for the diagnosis of prostate cancer (1). Despite various studies in the literature demonstrating low rates of complications and good tolerance to the procedure, it is still considered

invasive and not entirely free of complications (2, 3). Pain, mild hematuria, or hemospermia are common, self-limited, minor complications (4). Urinary tract infection (UTI or bacteremia, however, are potentially severe complications (5). Prophylactic antibiotic therapy and pre-biopsy enema are recommended for preventing infectious complications (6-8). Oral quinolones, either alone or in combination with other antibiotherapeutic agents, are the most common prophylactic practices. Unfortunately, in the last few years, increased resistance to quinolones has been reported in association with a rise in severe infectious complications after biopsy (9). In this study, we aimed to compare the incidence of prostatitis after prostate biopsy using two different prophylactic antibiotic protocols and provide an overview of the bacteriologic characteristics of urine and blood cultures, as well as antimicrobial resistance in NIH category I acute bacterial prostatitis.

MATERIALS AND METHODS

We reviewed the medical records of 3.479 patients TRUS-Bx cases performed between January 2011 and February 2016 in two different urology clinics of the same tertiary referral centre. Of these 3.479 patients, 437 cases underwent a repeat biopsy in case of a negative initial biopsy. The patients were elected from a PSA screening program that was applied in our hospital for patients in the age of fifty and afterwards once a year. Patients who were classified as underweighted (20kg/m2> body mass index (BMI)) and morbid obese (>35kg/m2) were excluded. Further patients with uncontrolled diabetes mellitus were also excluded. A specific matching procedure was not applied.

None of the patients had signs and symptoms of UTI or acute prostatitis before TRUS-Bx. The indications for TRUS-Bx were a PSA level >4.0ng/mL and abnormal findings in TRUS or by digital rectal exam (DRE). All procedures were performed with an 18-gauge core biopsy needle mounted on an automatic biopsy gun (Geotek Medical, Turkey) under local anaesthesia and ten core specimens were obtained in all biopsies. A blood test for prothrombin time and activated partial thromboplastin time were performed for all patients to obtain a coagulation profile. Patients were instructed not to take any oral anticoagulants in the last seven days before the TRUS-Bx procedure. Prophylactic treatment for TRUS-Bx was applied in two different regimens. The biopsy protocols were identical throughout the study period except for the prophylaxis regimen. Group I (n=1.523) received ciprofloxacin alone (500mg twice daily) continually for three days. Group II (n=1.956) received ciprofloxacin (500mg twice daily) plus ornidazole (500mg twice daily) for three days in addition to cleansing enema. Cleansing enema was applied one hour before the procedure.

A ll biopsies were performed in an outpatient department biopsy room by two doctors of each group. Acute prostatitis was diagnosed by a body temperature >38°C, positive urine analysis (bacteriuria and/or pyuria $>10^3$/mL), and pathologic, clinical findings by DRE. 5 Patients who developed acute prostatitis were admitted to hospital for treatment. Blood and urine samples were collected for bacterial evaluation before antimicrobial treatment was initiated. All organisms isolated from blood and urine cultures were tested for antimicrobial susceptibility. Informed consent was obtained from all patients before the biopsy procedure, and institutional approval was obtained for the study.

Cross-analysis with the chi-square test was performed to confirm the incidence rates of complications and their correlation between prophylactic treatment with only ciprofloxacin or ciprofloxacin plus ornidazole and cleansing enema. All statistical tests were two-sided with the significance level set at $P < 0.05$.

RESULTS

Mean age of the patients was 62.38 ± 7.30 (47-75) years. Descriptive statistics for the two different groups are presented in Table-1. Of the 3.479 patients, 39 (1.1%) patients developed acute prostatitis with symptoms within 1.28 (0-4) days after prostate biopsy. The patients with acute prostatitis symptoms were hospita-

Table 1 - Descriptive Statistics.

Variables	Ciprofloxacin group	Ciprofloxacin+ornidazole+ cleansing enema group	P-value
Age, year; mean ±SD (range)	62.1±7.4 (47-75)	62.34±7.19 (49-75)	0.61
BMI, kg/m^2; mean ±SD (range)	29.12±2.9 (20.7-33.8)	28.98±3.2 (20.3-34.4)	0.76
Prostate volume, mL; mean ±SD (range)	43.1±14.8 (21-91)	44.5±15.9 (22-100)	0.45
Preoperative PSA, ng/dL; mean±SD (range)	7.12±3.4 (2.4-95)	7.8±3.7(1.8-59)	0.53

lized and treated with two different intravenous antibiotics, including a third-generation cephalosporin (ceftriaxone) and an aminoglycoside (gentamicin) after urine and blood samples were taken for culture. The mean hospitalization time of acute prostatitis patients was 4.76±3.20 (2-20) days. Of the 39 patients, 15 (38%) had positive urine cultures, and of those, 13 (33%) had positive blood cultures. Both urine and blood cultures were negative in 24 (61%) of infected patients. Extended-spectrum beta-lactamase (ESBL)-producing E. coli were detected in 10 patients. Septic shock was observed in no patient and all patients cured after treatment.

The most frequent comorbidities were hypertension and DM (25.1% (n=875) and 16.7% (n=580), respectively). The rate of hypertension and DM in patients who developed acute prostatitis was 23% (n=9) and 17.9% (n=7), respectively. Hypertension or DM were not related to the development of acute prostatitis (P=0.76, X2=0.096 and P=0.83, X2=0.046, respectively). In Group I, in which only ciprofloxacin was used for prophylaxis, 22 of 1.522 (1.4%) patients developed acute prostatitis. In Group II, in which ciprofloxacin plus ornidazole and cleansing enema were used, 17 of 1.957 (0.8%) patients developed acute prostatitis. There was no statistical difference between the two groups according to acute prostatitis rate (X2=2.56, P=0.11). Of the 3.479 patients, 437 underwent a second biopsy. Acute prostatitis occurred after first and repeated biopsies in 28 (0.92%) and 11 (2.5%) patients, respectively (Table-2). The difference between the latter first and repeat biopsy groups according to the rate of acute prostatitis was statistically significant (P=0.001, X2=11.55).

DISCUSSION

In this study, we investigated the incidence of acute prostatitis under two different prophylactic regimens (ciprofloxacin alone or ciprofloxacin plus ornidazole with a cleansing enema) with bacteriologic characteristics of blood and urine cultures. Of the 3.479 patients, 39 (1.1%) developed acute prostatitis. Of these 39 patients, 15 (38%) had positive urine cultures, and 8 (20%) had positive blood cultures. According to our study, the rate of acute prostatitis was not statistically different between the two groups. Fluoroquinolones are one of the most effective antibiotics for the genitourinary system and show excellent penetration into the prostate tissue, and because the vast majority of uropathogens and enteric species have proper susceptibility to these agents, most of the trials have focused on fluoroquinolones (10-12). In the current study, ciprofloxacin was used as a prophylactic drug for Group I patients. Although frequently encountered uropathogens and coliforms such as E.coli or Klebsiella spp are usually responsible for the incidence of infectious complications after prostate biopsy, some infrequently encountered enteric pathogens, especially anaerobes, were reported in fever and septicemia after prostate biopsy, and the effects in the majority of these cases were severe and devasting (13, 14). Therefore, many studies have been conducted in the field of anaerobic coverage by prophylactic antibiotics during prostate biopsy (15, 16). Hence, as anaerobic bacteria coverage drug ornidazole was added to the ciprofloxacin prophylaxis therapy for Group II. It is widely accepted that antibiotic prophylaxis before TRUS-Bx is effective

Table 2 - Analysis of acute prostatitis cases in different prophylactic treatment regimes of transrectal postate biopsy. ESBL-Producing *E. Coli:* Extended-spectrum Beta-lactamase and Quinolone-resistant *Escherichia Coli*.

	Ciprofloxacin group	Ciprofloxacin+ornidazole+ cleansing enema group
Acute Prostatitis, n (%)	22 (1.4)	17 (0.8)
Symptoms starting time, days	1.28	1.32
Hospitalization time, day (mean±SD)	4.76±3.20	4.87±3.40
First Prostate Biopsy (n/N)	16/1320	12/1722
Second Prostate Biopsy (n/N)	6/203	5/234
Comorbidities		
HT	5	4
DM	4	3
Bacteria Culture		
Positive urinary culture, n (%)	7 (31.8)	8 (47)
Positive blood culture, n (%)	6(27.2)	7 (41)
ESBL- Producing *E. Coli*, n (%)	4 (18)	6 (35)
Blood culture ±	3/1	5/1

in preventing infectious complications (4). Despite the use of prophylactic antibiotics, bacterial infections causing fever, urinary tract infection, acute prostatitis and orchioepididymitis occur in 1-5% of patients (17, 18) Therefore, many researchers have attempted to identify the optimal prophylactic regimen to use peri-procedure, i.e. TRUS-Bx to decrease the risks of infectious complications. In this study, we investigated the incidence of acute prostatitis under two different prophylactic regimens (ciprofloxacin alone or ciprofloxacin plus ornidazole with a cleansing enema) with bacteriologic characteristics of blood and urine cultures. Intrarectal flora is disseminated within the prostate due to the insertion of biopsy equipment into the prostate through the rectum during TRUS-Bx. Theoretically, using prophylactic treatment for colonic flora may prevent infectious complications of the prostate. Fluoroquinolones (ciprofloxacin) are used most commonly as antibiotic prophylaxis due to their broad spectrum of antibacterial activity (17, 19). Other features include coverage for most aerobic microorganisms residing in the bowel, good oral bioavailability (70%-80%), extended half-life (4-5 hours), high concentration in both urine and prostate tissue, and post-antibiotic suppression of bacterial growth lasting for two to six hours (17). These features make ciprofloxacin a logical candidate to prevent prostatitis after prostate biopsy, however, the spread of fluoroquinolone resistance threatens to undermine the risk-benefit profile in transrectal prostate biopsy. The American Urological Association recommends prophylactic antibiotics within 24 hours of prostate biopsy for all patients, with a fluoroquinolone the antibiotic of choice (19). However, several studies have reported that acute prostatitis after TRUS-biopsy continues to occur, ranging from 1.3 to 9.3% (20, 21). In our study, ciprofloxacin was used as prophylactic treatment within 24 hours of prostate biopsy procedure and continued for three days after biopsy in Group I. Of these 1.523 patients, (22) (1.4%) developed acute prostatitis and were admitted to hospital for treatment within 1.28 (0-4) days following the prostate biopsy. Prophylactic antibiotic therapy and prebiopsy enema are recommended for preventing infectious complications (6). Ghafoori et al. conducted a study on 208 patients by categorizing them into either a povidone-iodine enema group or a control (no enema) group. A significant decrease in infectious complications was observed in patients who re-

ceived an enema (22). Kam et al. designed a study using 1.083 patients in which 658 (60.8%) had a prebiopsy enema in addition to prophylactic antibiotic treatment. Prebiopsy enema was done using glycerin or saline. Among these, 31 (4.7%) experienced complications. A prebiopsy enema was not performed in 425 patients (39.8%), of whom 38 (8.9%) had complications (p=0.007) (23). According to our study we only used fluoroquinolone in Group 1, nevertheless we found no significant difference in prostatitis rates between the two groups.

Ornidazole is a 5-nitroimidazole derivative and effective for anaerobic enteric pathogens, and it can be used as a prophylactic treatment before rectal surgery (24). In our study, ciprofloxacin, ornidazole, and cleansing enema were used as a prophylactic treatment in Group II patients, where 17 of 1.959 patients (0.8%) developed acute prostatitis. In this group, the prebiopsy enema was done using glycerin or saline. A Cochrane review concluded that enema plus antibiotics reduced the risk of bacteremia (relative risk [RR]: 0.25, 95% CI, 0.08-0.75) compared with antibiotics alone, but no differences were found in the rate of fever, or infection (25). The current study revealed no statistical difference according to acute prostatitis rates. In the presented study, 3.042 patients underwent a biopsy for the first time, and 437 had repeat biopsies. Acute prostatitis developed in 28 (0.92%) patients in the primary biopsy group and 11 (2.5%) patients in the repeat biopsy group. The risk of acute prostatitis was significantly higher after repeated biopsies. Similarly, Shigehara et al. investigated 457 patients, 371 underwent primary biopsy and 86 underwent repeat biopsy. Overall, acute bacterial prostatitis developed in six patients (1.3%). The rate of acute prostatitis after initial and repeat biopsies was 0.5% (n=2) and 4.7% (n=4). This result was statistically significant (26). Further Ozden et al. reported that a greater rate of acute prostatitis was observed in their repeat biopsy group than in patients who had undergone a prostate biopsy procedure for the first time (6.8% vs. 1.3%) (20). These studies concluded that repeat biopsies can be a risk factor for acute prostatitis. New biopsy technologies such as magnetic resonance imaging-transrectal ultrasonography (MRI-TRUS) fusion-guided-3D targeted biopsies have the potential to reduce the number of repeated biopsies (27). In cases of acute prostatitis, it is important to take blood and urine samples for culture. Song et al. reported that 63 of the 103 acute prostatitis cases (61.1%) had positive blood and/or urine cultures. In our study, the rate of positive urine and/or blood cultures was 58.9%, this result was higher compared with literature. We could not make a rational explanation for this difference.

Another critical concern is the emergence of quinolone-resistant Escherichia Coli (*E.coli*) and extended-spectrum beta-lactamases (ESBL)-producing E.coli strains. Song et al. reviewed 11.345 TRUS-Bx cases, and 63 cases of acute prostatitis were identified. ESBL producing E. coli strains were detected in 12 patients (20%). Three of the 12 patients had to be admitted to the intensive care unit and were treated successfully with intravenous ertapenem (28) In our study cohort, 39 patients developed infective symptoms after prostate biopsy.

Suzuki et al. conducted a study on DM patients in which they performed prostate biopsy using the transperineal approach. They concluded that transperineal biopsy could be carried out without major infectious complications in DM men (29). In our study population, seven of 39 prostatitis patients had DM. Our results revealed that DM was not related to acute prostatitis. Besides, hypertension was also not associated with the occurrence of acute prostatitis.

A limitation of the study is that the it involves two different cohorts from two different clinics, as a result, slight diagnostic difference may have affected the results. Another weakness is that some patients in which complications occurred could have been be treated in other hospitals. Further, the retrospective design is a limitation. More reliable results would be obtained in prospective randomized study design.

In conclusion, repeat biopsies can increase the acute prostatitis risk after TRUS-Bx. The use of prebiopsy cleansing enema with ornidazole treatment in addition to ciprofloxacin prophylaxis did not decrease the acute prostatitis risk. Although resistance to fluoroquinolones has increased over the years, the use of antibiotics effective for anaerobic pathogens seems not to be essential yet.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011;59:61-71.
2. Shigemura K, Tanaka K, Yasuda M, Ishihara S, Muratani T, Deguchi T, et al. Efficacy of 1-day prophylaxis medication with fluoroquinolone for prostate biopsy. World J Urol. 2005;23:356-60.
3. Tobias-Machado M, Corrêa TD, De Barros EL, Wroclawski ER. Antibiotic prophylaxis in prostate biopsy. A comparative randomized clinical assay between ciprofloxacin, norfloxacin and chloramphenicol. Int Braz J Urol. 2003;29:313-9.
4. Campeggi A, Ouzaid I, Xylinas E, Lesprit P, Hoznek A, Vordos D, et al. Acute bacterial prostatitis after transrectal ultrasound-guided prostate biopsy: epidemiological, bacteria and treatment patterns from a 4-year prospective study. Int J Urol. 2014;21:152-5.
5. Djavan B, Waldert M, Zlotta A, Dobronski P, Seitz C, Remzi M, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. J Urol. 2001;166:856-60.
6. Rodríguez LV, Terris MK. Risks and complications of transrectal ultrasound guided prostate needle biopsy: a prospective study and review of the literature. J Urol. 1998;160(6 Pt 1):2115-20.
7. Kim SJ, Kim SI, Ahn HS, Choi JB, Kim YS, Kim SJ. Risk factors for acute prostatitis after transrectal biopsy of the prostate. Korean J Urol. 2010;51:426-30.
8. Brown RW, Warner JJ, Turner BI, Harris LF, Alford RH. Bacteremia and bacteriuria after transrectal prostatic biopsy. Urology. 1981;18:145-8.
9. Al-Hasan MN, Lahr BD, Eckel-Passow JE, Baddour LM. Antimicrobial resistance trends of Escherichia coli bloodstream isolates: a population-based study, 1998-2007. J Antimicrob Chemother. 2009;64:169-74.
10. Lugg J, Lettieri J, Stass H, Agarwal V. Determination of the concentration of ciprofloxacin in prostate tissue following administration of a single, 1000 mg, extended-release dose. J Chemother. 2008;20:213-8.
11. Lindstedt S, Lindström U, Ljunggren E, Wullt B, Grabe M. Single-dose antibiotic prophylaxis in core prostate biopsy: Impact of timing and identification of risk factors. Eur Urol. 2006;50:832-7.
12. Naber KG, Sörgel F. Antibiotic therapy--rationale and evidence for optimal drug concentrations in prostatic and seminal fluid and in prostatic tissue. Andrologia. 2003;35:331-5.
13. Webb NR, Woo HH. Antibiotic prophylaxis for prostate biopsy. BJU Int. 2002;89:824-8.
14. Brewster SF, Rooney N, Kabala J, Feneley RC. Fatal anaerobic infection following transrectal biopsy of a rare prostatic tumour. Br J Urol. 1993;72:977-8.
15. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. BJU Int. 2000;85:682-5.
16. Breslin JA, Turner BI, Faber RB, Rhamy RK. Anaerobic infection as a consequence of transrectal prostatic biopsy. J Urol. 1978;120:502-3.
17. Kapoor DA, Klimberg IW, Malek GH, Wegenke JD, Cox CE, Patterson AL, et al. Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. Urology. 1998;52:552-8.
18. Rietbergen JB, Kruger AE, Kranse R, Schröder FH. Complications of transrectal ultrasound-guided systematic sextant biopsies of the prostate: evaluation of complication rates and risk factors within a population-based screening program. Urology. 1997;49:875-80.
19. Wolf JS Jr, Bennett CJ, Dmochowski RR, Hollenbeck BK, Pearle MS, Schaeffer AJ, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol. 2008;179:1379-90.
20. Ozden E, Bostanci Y, Yakupoglu KY, Akdeniz E, Yilmaz AF, Tulek N, et al. Incidence of acute prostatitis caused by extended-spectrum beta-lactamase-producing Escherichia coli after transrectal prostate biopsy. Urology. 2009;74:119-23.
21. Mosharafa AA, Torky MH, El Said WM, Meshref A. Rising incidence of acute prostatitis following prostate biopsy: fluoroquinolone resistance and exposure is a significant risk factor. Urology. 2011;78:511-4.
22. Ghafoori M, Shakiba M, Seifmanesh H, Hoseini K. Decrease in infection rate following use of povidone-iodine during transrectal ultrasound guided biopsy of the prostate: a double blind randomized clinical trial. Iran J Radiol. 2012;9:67-70.
23. Kam SC, Choi SM, Yoon S, Choi JH, Lee SH, Hwa JS, et al. Complications of transrectal ultrasound-guided prostate biopsy: impact of prebiopsy enema. Korean J Urol. 2014;55:732-6.

24. McArdle CS, Morran CG, Pettit L, Gemmell CG, Sleigh JD, Tillotson GS. Value of oral antibiotic prophylaxis in colorectal surgery. Br J Surg. 1995;82:1046-8.
25. Zani EL, Clark OA, Rodrigues Netto N Jr. Antibiotic prophylaxis for transrectal prostate biopsy. Cochrane Database Syst Rev. 2011;(5):CD006576.
26. Shigehara K, Miyagi T, Nakashima T, Shimamura M. Acute bacterial prostatitis after transrectal prostate needle biopsy: clinical analysis. J Infect Chemother. 2008;14:40-3.
27. Sonn GA, Natarajan S, Margolis DJ, MacAiran M, Lieu P, Huang J, et al. Targeted biopsy in the detection of prostate cancer using an office based magnetic resonance ultrasound fusion device. J Urol. 2013;189:86-91.
28. Song W, Choo SH, Sung HH, Han DH, Jeong BC, Seo SI, et al. Incidence and management of extended-spectrum beta-lactamase and quinolone-resistant Escherichia coli infections after prostate biopsy. Urology. 2014;84:1001-7.
29. Suzuki M, Kawakami S, Asano T, Masuda H, Saito K, Koga F, et al. Safety of transperineal 14-core systematic prostate biopsy in diabetic men. Int J Urol. 2009;16:930-5.

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EDITORIAL COMMENT

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Editorial Comment: Acute prostatitis after prostate biopsy under ciprofloxacin prophylaxis with or without ornidazole and pre-biopsy enema: analysis of 3.479 prostate biopsy cases

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With great relevance, the International Brazilian Journal of Urology brings to its readers important material that points us to the dreaded complication inherent in transrectal ultrasound-guided prostate biopsy (TRUS-Bx) and the role of antibiotic prophylaxis against prostatitis (1). In their results, the authors demonstrated that cleasing enema did not change the outcome when comparing the groups. It has been reported a significantly lower rate of complications by administering glycerin or saline enema 1h before TRUS-Bx (2) although a randomized study has shown that the use of iodine-povidine solution would not have the potential to reduce the risk of prostatitis with statistical significance (3).

It should be agreed that even if it does not make the procedure aseptic, local hygiene is part of good practices, with low cost and adequate tolerability. In our clinical routine, we provide the patient, at the time of the biopsy indication, a glycerin suppository to be introduced into the rectum the night before the procedure. Among the advantages of this tactic, the patient can arrive with the empty rectum the next morning, and still facilitate the introduction of the probe by additional lubrication performed also with transrectal 2% lidocaine jelly anestesia after patient's sedation.

The number of samples collected and the diameter of the needle was also the subject of concern on the correlation with infection after TRUS-Bx. Authors used the 18G needle and harvesting of 10 fragments under local anesthesia.

Although studies suggest sampling with 12 to 18 fragments (4), the latest UAE recommendations propose that at least eight systematic biopsies are recommended in prostates with a size of about 30 cc and ten to twelve core biopsies are recommended in larger prostates (5). Ultrasound-guided periprostatic block is recommended (6) and is not related with increase rates of prostatitis (7).

Although bacterial resistance to ciprofloxacin is well reported (8-10), this drug still represents an affordable and effective option in the context of prostate biopsy prophylaxis against infections. As in our daily practice at the National Cancer Institute's Prostate Cancer Diagnostic Center, group 1 used ciprofloxacin for a total of four days. Statistical analysis have shown that addition of the second drug (ornidazole) did not significantly reduce the rate of prostatitis. In a public health scenario, this information is relevant as it allows us to save resources that could be used for other inputs.

Also regarding the relevant results, the authors report us the increased incidence of acute prostatitis in those individuals who underwent multiple TRUS-Bx.

This may be the outmost data brought in this paper. Realize how current this information is and why it should be highlighted: understanding that we are increasingly diagnosing individuals in the early stages of the disease and that management through active surveillance includes serial biopsies; when recommending subsequent procedures, the practitioner should be extremely alert to signs of complications and the patient should be aware of this increased risk (11).

Multiparametric MRI (mpMRI) is part of the active surveillance protocol for prostate cancer and has the potential to improve accuracy through ultrasound-guided target biopsies e and reduce overall complications (8, 12). Some authors evaluated it's use even in virgin individuals from previous biopsies (13), but neither the European (EAU/ ESTRO/SIOG/ESUR) nor the American (NCCN) guidelines endorse wholeheartedly mpMRI in biopsy-naïve men (14, 15). Using this technology to reduce the number of samples collected could virtually reduce complications associated to the procedure.

The authors acknowledged some limitations of their study, which indicates an important commitment of that team regarding the scientific communication. In this sense, I propose to the reader to remember that local realities sometimes determine specific behaviors not always aligned with international guidelines. In developing countries, limited access to health technologies is a clear sign of the social disparity of these societies. There are cases in which patients come to the diagnostic procedure already in a degrading state of health, sometimes catheterized and with UTI; in other cases, after the biopsy has been performed and the prescription provided, the patient has no way to get the drugs. These are everyday situations and it is up to us to make the best medical art, *primum non nocere*.

It is wonderful that we have advanced the level of knowledge and that humanization in health has reached the core of the most mustached urologists; but our efforts will be worthless if health access policies are not improved.

REFERENCES

1. Balaban M, Ozkaptan O, Sevinc C, Boz MY, Horuz R, Kafkasli A, Canguven O. Acute prostatitis after prostate biopsy under ciprofloxacin prophylaxis with or without ornidazole and prebiopsy enema: analysis of 3.479 prostate biopsy cases. Int Braz J Urol. 2020;46:60-6.
2. Kam SC, Choi SM, Yoon S, Choi JH, Lee SH, Hwa JS, et al. Complications of transrectal ultrasound-guided prostate biopsy: impact of prebiopsy enema. Korean J Urol. 2014;55:732-6.
3. Abughosh Z, Margolick J, Goldenberg SL, Taylor SA, Afshar K, Bell R, et al. A prospective randomized trial of povidone-iodine prophylactic cleansing of the rectum before transrectal ultrasound guided prostate biopsy. J Urol. 2013;189:1326-31.
4. Roberts MJ, Bennett HY, Harris PN, Holmes M, Grummet J, Naber K, et al. Prostate Biopsy-related Infection: A Systematic Review of Risk Factors, Prevention Strategies, and Management Approaches. Urology. 2017;104:11-21.
5. Lam TBL, MacLennan S, Willemse PM, Mason MD, Plass K, Shepherd R, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). Eur Urol. 2019;76:790-813.
6. von Knobloch R, Weber J, Varga Z, Feiber H, Heidenreich A, Hofmann R. Bilateral fine-needle administered local anaesthetic nerve block for pain control during TRUS-guided multi-core prostate biopsy: a prospective randomised trial. Eur Urol. 2002;41:508-14.
7. Bruyère F, Malavaud S, Bertrand P, Decock A, Cariou G, Doublet JD, et al. Prosbiotate: a multicenter, prospective analysis of infectious complications after prostate biopsy. J Urol. 2015;193:145-50.
8. Borghesi M, Ahmed H, Nam R, Schaeffer E, Schiavina R, Taneja S, et al. Complications After Systematic, Random, and Image-guided Prostate Biopsy. Eur Urol. 2017;71:353-65.
9. Wagenlehner FM, van Oostrum E, Tenke P, Tandogdu Z, Çek M, Grabe M, et al. Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. Eur Urol. 2013;63:521-7.
10. Walker JT, Singla N, Roehrborn CG. Reducing Infectious Complications Following Transrectal Ultrasound-guided Prostate Biopsy: A Systematic Review. Rev Urol. 2016;18:73-89.
11. Ehdaie B, Vertosick E, Spaliviero M, Giallo-Uvino A, Taur Y, O'Sullivan M, et al. The impact of repeat biopsies on infectious complications in men with prostate cancer on active surveillance. J Urol. 2014;191:660-4.
12. Richenberg J, Løgager V, Panebianco V, Rouviere O, Villeirs G, Schoots IG. The primacy of multiparametric MRI in men with suspected prostate cancer. Eur Radiol. 2019;29:6940-52.
13. Lebastchi AH, Pinto PA. The role of multiparametric MRI in biopsy-naive prostate cancer. Nat Rev Urol. 2019;16:276-7.

14. Westerman ME, Sharma V, Bailey GC, Boorjian SA, Frank I, Gettman MT, et al. Impact of time from biopsy to surgery on complications, functional and oncologic outcomes following radical prostatectomy. Int Braz J Urol. 2019;45:468-77.
15. Sasse AD, Dos Reis RB, Nogueira LM, Maluf FC, Herchenhorn D, Smaletz O, et al. Second brazilian consensus on the treatment of advanced prostate cancer - a SBOC-SBU-SBRT panel review. Int Braz J Urol. 2019;45:449-58.

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Upper urinary tract stone compositions: the role of age and gender

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ABSTRACT

Objective: To analyze the compositions of upper urinary tract stones and investigate their distributions in different gender and age groups.
Materials and Methods: Patients diagnosed with upper urinary tract stone disease between December 2014 and March 2018 were retrospectively reviewed. Patient's age, gender, BMI, comorbidities, stone event characteristics, and compositions were collected, and proportions of stone components in different gender and age groups were analyzed.
Results: A total of 1532 stone analyses were performed (992 from males and 540 from females). The mean age was younger in males ($p < 0.001$). Males included more cases with larger BMI, hyperuricemia, and obesity, while females had more urinary tract infections. Multiple components were present in 61.8% of stones. Calcium oxalate (CaOx) (67.0%) was the most common component, followed by uric acid (UA) (11.8%), infection stone (11.4%), calcium phosphate (CaP) (8.0%), cystine (1.1%), brushite (0.4%), and 2,8-dihydroxyadenine (0.2%). Men contributed with more CaOx stones than women at age 30-49 years (all $p < 0.01$) and more UA stones at 30-59 years (all $p < 0.05$). Women contributed with more infection stones than men in age groups 30-49 and 60-69 years (all $p < 0.05$), and more CaP stones at 30-49 years. The prevalence peak was 50-59 years in men and 60-69 years in women. Both genders had the lowest prevalence in adolescence. Prevalence of UA stones increased while that of infection stones decreased with aging in both genders.
Conclusions: Age and sex had a strong association with distribution of stone compositions in this Chinese cohort.

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INTRODUCTION

The prevalence of urolithiasis is increasing in both developed and developing countries. Studies have demonstrated that ethnicity, geographic region, and living conditions could have an influence on stone formation (1). A recent study based on the United States population demonstrated that demographic factors, especially gender and age, had potential effects on stone composition, reporting that younger women had more hydroapatite stones, whereas older individuals were more susceptible to uric acid stones (2). Other studies from Europe have confirmed a higher prevalence of uric acid stone formation in the older population (3, 4).

However, most of these studies were from Western countries and focused on Caucasians. Relatively little has been reported about the function of age and gender on stone composition in the Chinese population, and these published studies were conducted in local hospitals in southern and eastern areas. As one of the largest stone management institutes in northern China, we reviewed a large cohort of stone analysis reports from the last 3 years and investigated the possible association of age and gender with stone composition from an epidemiological perspective.

MATERIALS AND METHODS

Data collection

Patients diagnosed with upper urinary stone disease in Beijing Tsinghua Changgung Hospital from December 2014 to March 2018 were included. Only data from patients whose stones were retrieved intraoperatively (ureteroscopy and percutaneous nephrolithotomy) and sent for analysis were collected. Patient's demographic information such as age, gender, body mass index (BMI), and comorbidities were gathered. We also included history of lithotripsy and urinary tract infection (UTI), stone location, surgical approaches for stone acquisition, and stone composition for evaluation of stone episodes.

Stone composition analysis

All stone samples gathered from the operation were analyzed in the stone analysis laboratory by infrared spectroscopy. After the specimens were washed, dried, and pulverized, 1mg was mixed with 100-200mg of potassium bromide into a uniform powder, and then laminated into a test slice to be placed in an infrared spectrum automatic analysis system for detection. The principal component of the stone was recorded, the classification criteria for which were as follows (2, 5, 6): calcium oxalate (CaOx) stone refers to that with any kind of CaOx >50%; calcium phosphate (CaP) stone contains >50% CaP; infection stone contains >10% magnesium ammonium phosphate or ammonium urate; uric acid (UA) stone contains >50% UA; brushite, cystine, and other rare compositions. For example, if the stone was composed of 40% calcium oxalate monohydrate (COM), 30% calcium oxalate dehydrate (COD), and 30% CaP, it would be considered as a CaOx stone. If the sample was found to consist of 20% magnesium ammonium phosphate, 60% CaP, and 20% COM, it would be classified as an infection stone.

STATISTICAL METHODS

Patients were divided into nine age groups by 10-year intervals. The prevalence of stone components was evaluated by two parameters: proportion and the prevalence ratio adjusted by the population of China census in 2017. The prevalence of stone in females at age 0-9 years was chosen as the reference. Statistical analysis was conducted using SPSS 22.0 for Windows (SPSS, Chicago, IL, USA). The proportions of categorical variables were analyzed using the Chi-square test and Fisher's exact test. Uni-and multivariate logistic regression analyses were performed to evaluate the risk factors contributing to stone composition conversion. $P < 0.05$ was considered statistically significant.

RESULTS

Between December 2014 and March 2018, 1532 stone analyses were performed, 992 of which were from males and 540 from females. The mean age was younger in males than in females (45.9 vs. 50.0 years, $p < 0.001$). Males included more cases with larger BMI, hyperuricemia, and obesity (BMI ≥30kg/m2), while females had more UTIs (Table-1). More kidney stones and percutaneous nephrolithotomies (PCNL) were seen in females ($p < 0.001$). A total of 948 (61.8%) stones were composed of multiple elements, to which women contributed much more than males (70.9% vs. 57.0%, $p < 0.001$). CaOx (67.0%) was the most common component, followed by UA (11.8%), infection stone (11.4%), CaP (8.0%), cystine (1.1%), brushite (0.4%), and 2,8-dihydroxyadenine (0.2%). The four most common stone compositions in men were CaOx stone (69.8%), UA stone (13.8%), infection stone (8.3%), and CaP stone (6.5%), while in women they were CaOx stone (62.0%), infection stone (17.1%), CaP stone (10.9%), and UA

Table 1 - Characteristics of patients and stone compositions stratified by gender.

Parameters	Total number N=1532	Stones from Males N=992	Stones from Females N=540	p-value
Age (year, mean±SD)	47.4±16.4	45.9±17.1	50.0±14.7	<0.001
BMI (kg/m^2)	25.9±3.4	27.4±3.2	24.9±3.5	0.011
Comorbidities				
Hypertension	329 (21.5%)	219 (22.1%)	110 (20.4%)	0.473
Diabetes	206 (13.4%)	128 (12.9%)	78 (14.4%)	0.398
Hyperuricemia	213 (13.9%)	151 (15.2%)	62 (11.5%)	0.043
Obesity (BMI ≥30kg/m^2)	277 (18.1%)	200 (20.1%)	77 (14.3%)	0.004
History of lithotripsy				
No	952 (62.1%)	607 (61.2%)	345 (63.9)	0.298
ESWL	241 (15.7%)	152 (15.3%)	89 (16.5%)	0.552
Ureteroscopy	153 (10.0%)	95 (9.6%)	58 (10.7%)	0.468
PCNL	214 (14.0%)	138 (13.9%)	76 (14.1%)	0.930
Open or laparoscopic nephrolithotomy	55 (3.6%)	41 (4.1%)	14 (2.6%)	0.122
Urinary tract infection	547 (35.7%)	336 (33.9%)	211 (39.1%)	0.042
Episode				
First	866 (56.5%)	555 (55.9%)	311 (57.6%)	0.535
Recurrent	666 (43.5%)	437 (44.1%)	229 (42.4%)	
Stone location				
Kidney	1128 (73.6%)	768 (77.4%)	460 (85.2%)	<0.001
Ureter	304 (26.4%)	224 (22.6%)	80 (14.8%)	
Surgery of stone acquisition				
Ureteroscopy	722 (47.1%)	493 (49.7%)	229 (42.4%)	0.006
PCNL	810 (52.9%)	499 (50.3%)	311 (57.6%)	
Composition				
Single	584 (38.2%)	427 (43.0%)	157 (29.1%)	<0.001
Mixed	948 (61.8%)	565 (57.0%)	383 (70.9%)	
Stone compositions				
Calcium oxalate	1027 (67.0%)	692 (69.8%)	335 (62.0%)	0.001
Infection stone	175 (11.4%)	82 (8.3%)	93 (17.2%)	<0.001
Calcium phosphate	123 (8.0%)	64 (6.5%)	59 (10.9%)	0.002
Uric acid	181 (11.8%)	137 (13.8%)	44 (8.1%)	0.001
Cystine	17 (1.1%)	10 (1.0%)	7 (1.3%)	/
2.8-Dihydroxyadenine	3 (0.2%)	3 (0.3%)	0	/
Brushite	6 (0.4%)	4 (0.4%)	2 (0.4%)	/

stone (8.1%) (Figure-1). The proportions of CaOx (p=0.002) and UA (p=0.002) were much higher in men than in women, whereas the proportions of infection stone (p <0.001) and CaP (p=0.002) were much higher in women.

The age-specific prevalence ratios showed that the lowest prevalence for both males and females was in their adolescence, and the peak of prevalence was observed during the age of 50-59 years in men and 60-69 years in women (Table-2). Men presented more CaOx stones than women in the 30-49 years (all p <0.05), and more UA stones at age 30-59 years (p <0.05 for all). Women accounted for more infection stones than men between the ages of 30-49 and 60-69 years (all p <0.05), and more CaP stones at age 30-49 years (Table-3). The prevalence of UA stones was higher in both genders after their 40s.

We further analyzed stone conversions in different episodes. A total of 118 patients with two stone episodes and surgical removal of stones were identified in our center, of whom 48 (40.7%) had stone conversions in the second episode. Multivariate analysis showed that only CaP in the first episode (OR 14.178, 95%CI 2.655-75.702, p=0.002) was associated with stone conversion in the second episode, after controlling for age, gender, and the procedure for the first episode (Supplementary Tables).

DISCUSSION

Urinary stone disease is a common disorder worldwide, causing severe socioeconomic and healthcare burden. Approximately 1 in 11 people in the United States will be affected by urinary stones during their lifetime (7). The incidence of urolithiasis in China has been increasing steadily during the last 20 years, mainly because of changing of lifestyles factors, especially diet (8). The most recent nationwide study revealed that about 1 in 17 adults in China has renal stones (9).

Urolithiasis is reported to be a male-dominant disease with an estimated male-to-female ratio ranging from 1.7:1 to 3:1 (10-12). We also observed a male dominance pattern with a ratio of 1.8 in our study. Stone compositions differed significantly between genders. Men presented more CaOx and UA stones than women, consistent with recent studies in other parts of China (13, 14). Males had a tendency to consume more animal meat and proteins, thus developing oversaturated CaOx

Figure 1 - Proportions of stone compositions in different age groups and genders.

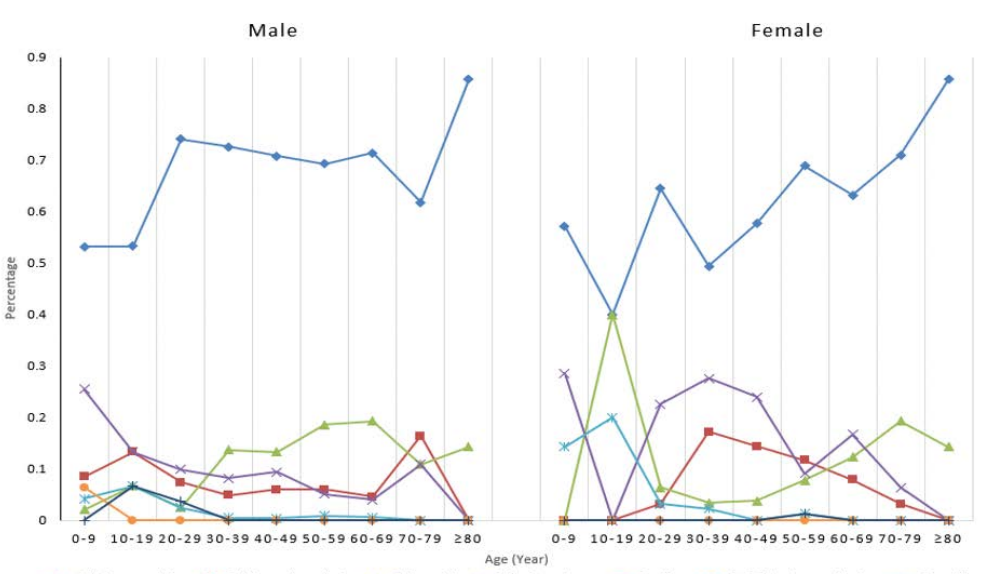

Table 2 - Age-specific prevalence ratios adjusted by the population of China census in 2017.

Age Groups (years)	Number of Patients		Population Percentage (Vintage 2017)		M/F Population Ratio	Age-specific Incidence Ratio	
	M	F	M	F		M	F
0-9	47 (3.1%)	7 (0.5%)	6.3%	5.5%	1.15	5.86	1 (Ref.)*
10-19	15 (1.0%)	5 (0.3%)	5.8%	5%	1.16	2.03	0.79
20-29	81 (5.3%)	31 (2.0%)	8.3%	7.5%	1.11	7.67	3.25
30-39	182 (11.9%)	87 (5.7%)	7.6%	7.1%	1.07	18.82	9.63
40-49	233 (15.2%)	104 (6.8%)	8.6%	8.2%	1.05	21.29	9.97
50-59	215 (14.0%)	154 (10.1%)	7.1%	6.9%	1.03	23.79	17.54
60-69	150 (9.8%)	114 (7.4%)	5%	5%	1.00	23.57	17.91
70-79	55 (3.6%)	31 (2.0%)	2.1%	2.2%	0.95	20.58	11.07
≥80	14 (0.9%)	7 (0.5%)	0.5%	1%	0.80	13.75	5.5
Total	**992 (64.8%)**	**540 (35.2%)**	**51.6%**	**48.4%**	**1.07**	**15.11**	**8.77**

*Reference: The prevalence of stone in females in age 0-9 years.

and UA in the urine (15). It is worth noting that males had more cases with larger BMI, hyperuricemia, and obesity in our study population, which might be one reason for such a pattern.

The prevalence of infection stones among women in our study was two times of that in men (17.22% vs. 8.27%). Women are known to be at higher risk of developing UTIs, which in turn will elevate urinary pH and facilitate the growth of organisms containing urease (16). Younger females are observed to possess a higher urine pH (14), which could explain why in our study the prevalence of infectious stones was higher in women aged 30-49 years and lower in older age groups. Overall, the rate of infectious stones observed in our center was much higher than in any other centers in China. As a tertiary hospital, our institution manages more complex stone cases with severe infection and staghorn stones, which may lead to a selection bias. CaP, the second most common stone component in females, is associated with renal acidification defects, calcium or phosphate metabolic disturbance, and UTI (17). The theory that CaP is formed in alkaline urine (18) could support our finding of the disparity between genders because women generally possess urine of higher pH.

We observed component discrepancies among different age groups. Men submitted more CaOx stones than women at age 30-49 years, more UA stones at age 30-59 years, fewer infection stones at age 30-59 years, and fewer CaP stones at age 30-49 years. Although CaOx was the most common component in both genders, peaking at 30-69 years, differences have been observed between continents, with CaOx peaking at 40-50 years of age in Europe and 16-39 years in northern Africa. Wu et al. reported a peak age for CaOx stones at 19-40 years in southern China (13), whereas Yang et al. reported a prevalence peak of 30-50 years in eastern China (14). Ethnicity, different dietary preferences, and population composition may contribute collectively to create such disparity.

UA has been reported to have increased dramatically in recent years. Wu et al. reported that compared with 2003-2007, the number of UA stones in 2008-2012 doubled (3.83% vs. 6.94%)

Table 3 - Proportions of different stone compositions stratified by age groups.

	Total	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	≥80
Calcium oxalate	1027	29 (2.8%)	10 (1.0%)	80 (7.8%)	175 (17.0%)	225 (21.9%)	255 (24.8%)	179 (17.4%)	56 (5.5%)	18 (1.8%)
Male	692	25 (3.6%)	8 (1.2%)	60 (8.7%)	132 (19.1%)	165 (23.8%)	149 (21.5%)	107 (15.5%)	34 (8.1%)	12 (1.7%)
Female	335	4 (1.2%)	2 (0.6%)	20 (6.0%)	43 (12.8%)	60 (17.9%)	106 (31.6%)	72 (21.5%)	22 (6.6%)	6 (1.8%)
p-value		0.585	0.5	0.316	<0.001	0.018	0.923	0.159	0.393	0.753
Calcium phosphate	123	4 (3.3%)	2 (1.6%)	7 (5.7%)	24 (19.5%)	29 (23.6%)	31 (25.2%)	16 (13.0%)	10 (8.1%)	0
Male	64	4 (6.3%)	2 (3.1%)	6 (9.4%)	9 (14.1%)	14 (21.9%)	13 (20.3%)	7 (10.9%)	9 (14.1%)	0
Female	59	0	0	1 (1.7%)	15 (25.4%)	15 (25.4%)	18 (30.5%)	9 (15.3%)	1 (1.7%)	0
p-value		0.564	0.553	0.374	0.001	0.011	0.054	0.276	0.064	/
Uric acid	181	1 (0.6%)	3 (1.7%)	4 (2.2%)	28 (15.5%)	35 (19.3%)	52 (28.7%)	43 (23.8%)	12 (6.6%)	3 (1.7%)
Male	137	1 (0.7%)	1 (0.7%)	2 (1.5%)	25 (18.2%)	31 (22.6%)	40 (29.2%)	29 (21.2%)	6 (4.4%)	2 (1.5%)
Female	44	0	2 (4.5%)	2 (4.5%)	3 (6.8%)	4 (9.1%)	12 (27.3%)	14 (31.8%)	6 (13.6%)	1 (2.3%)
p-value		0.87	0.14	0.306	0.01	0.009	0.003	0.124	0.221	0.726
Infection stone	175	14 (8.0%)	2 (1.1%)	15 (8.6%)	39 (22.3%)	47 (26.9%)	25 (14.3%)	25 (14.3%)	8 (4.6%)	0
Male	82	12 (14.6%)	2 (2.4%)	8 (9.8%)	15 (18.3%)	22 (26.8%)	11 (13.4%)	6 (7.3%)	6 (7.3%)	0
Female	93	2 (2.2%)	0	7 (7.5%)	24 (25.8%)	25 (26.9%)	14 (15.1%)	19 (20.4%)	2 (2.2%)	0
p-value		0.591	0.553	0.076	<0.001	<0.001	0.134	<0.001	0.396	/
Others*	26	6 (23.1%)	3 (11.5%)	6 (23.1%)	3 (11.5%)	1 (3.8%)	6 (23.1%)	1 (3.8%)	0	0
Male	17	5 (29.4%)	2 (11.8%)	5 (29.4%)	1 (5.9%)	1 (5.9%)	2 (11.8%)	1 (5.9%)	0	0
Female	9	1 (11.1%)	1 (11.1%)	1 (11.1%)	2 (22.2%)	0	4 (44.4%)	0	0	0

*Others included cystine stone, 2,8-dihydroxyadenine, and brushite.

(13). In our study, UA contributed to 11.8% of all stones, which was almost the same as that reported by a recent study in China in 2019, with a UA stone prevalence of 11.1% (9). We also found that the prevalence of UA stones slowly increased among both genders with aging (2). UA stones have a close association with metabolic syndrome and renal insufficiency, which are more prevalent in older people than in the younger generation (19). Increased acidic urine observed in elderly patients can lead to renal proximal tubular injury and impaired tubular alkalization (20), predisposing older people to UA stones.

Studies have demonstrated that the metabolic changes after the menopause might have an influence on urine components, increasing the risk of stone formation in this population. Prochaska et al. reported a higher risk of renal stones in postmenopausal women (OR 1.27, 95% CI 1.08-1.46) (21). Zhao et al. demonstrated that postmenopausal women were predisposed to urinary stones with lower blood estrogen (22), and Heller et al. reported that postmenopausal women who were treated with estrogen had lower 24h calcium excretion and CaOx saturation (23). In our study, we did observe an increasing prevalence of stone disease in women after their 50s. As women reached their 70s and 80s the proportions of stone components become similar to those of men, in another way supporting the notion that the menopause might have an influence on stone formation. Based on our data, we were unable to conclude whether the menopause is an independent risk factor for stone formation, since details such as menstrual status, level of serum estrogen, urine metabolic analysis, and lifestyle and dietary changes in older females were not available in our study population.

Generally, the prevalence of urinary stones in children is much lower than that in adults, with reported rates of 2% to 5% (24). However, stone formation can precede a high rate of recurrence and considerable morbidity in children. In our study, incidences for both genders were relatively high in their first decade and decreased as they entered adolescence. Genetic and metabolic disorders are common in children with urinary stone diseases, with hypercalciuria and hypocitraturia being the most prevalent (24). In a study conducted in southern China, stones from 382 children included 78.8% CaOx, 10.7% infection stones, 9.4% cystine, and 1.1% UA, of which 97.5% of the patients manifested as low citrate (25). Differences have been observed among different areas within China. One study from eastern China reported a relatively high rate of CaOx and cystine stones, and a low rate of struvite stones in children (26), while a study in the northwest border region reported ammonium urate as the dominant stone component in the whole population (27). An early study in Argentina reported that 84.4% of the children with urinary stone disease had metabolic abnormalities, with hypercalciuria and hypocitraturia being the two major risk factors (24). Twenty-four-hour urine analysis and genetic tests are recommended strongly for children with early onset of urinary stone disease to evaluate possible metabolic and genetic disorders and target the treatment to reduce recurrence (28).

Drug-and food-induced urinary tract stones are much more common in children. In 2008, China experienced an event of melamine contamination of powdered-milk formula for infants (29). When the concentration of melamine from the formula was sufficiently high in the urine, it easily formed crystals or stones in the infants because of its low solubility (30). The stones analyzed during this crisis were proved to be composed of uric acid dihydrate and ammonium urate (26). It is incumbent on urologists to apply the new knowledge of such rare etiology to the improvement of medical care treatment of children.

The present study was one of the very few that investigated the effects of age and gender on stone compositions among the Chinese population. However, some limitations are apparent. First, although we compared the prevalence ratios between age groups adjusted by the population proportions, the actual prevalence of the urinary stone disease in the real world could not be calculated because the data were gathered from patients with urolithiasis. Second, all stone samples were retrieved from operations, leading to a bias against the existence of an unknown number of patients with asymptomatic stones or experiencing spontaneous stone passage away from the hospital. Third, our department admitted mainly

adult patients, which could also introduce bias regarding the evaluation of children. Lastly, because of the retrospective study design, we were unable to gather information such as 24-hour urine analysis. It may be concluded that age and gender represent the epidemiological features, not the direct functional factor. Further well-designed multicenter studies are needed to better elucidate the mechanisms behind these differences.

CONCLUSIONS

In conclusion, our study presented an analysis of stone compositions in a large population in northern China. Significant disparities of stone compositions existed among different genders and ages. Overall, males submitted more CaOx and UA stones whereas females were susceptible to CaP and infectious stones. Incidence of UA stones increased with aging while that of infection stones decreased. The underlying mechanism, including metabolic differences and the function of estrogen, needs to be investigated in the future.

ETHICAL APPROVAL

The protocol was approved by the institutional ethics committee.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Clayton DB, Pope JC. The increasing pediatric stone disease problem. Ther Adv Urol. 2011;3:3-12.
2. Lieske JC, Rule AD, Krambeck AE, Williams JC, Bergstralh EJ, Mehta RA, et al. Stone composition as a function of age and sex. Clin J Am Soc Nephrol. 2014;9:2141-6.
3. Knoll T, Schubert AB, Fahlenkamp D, Leusmann DB, Wendt-Nordahl G, Schubert G. Urolithiasis through the ages: data on more than 200,000 urinary stone analyses. J Urol. 2011;185:1304-11.
4. Daudon M, Doré JC, Jungers P, Lacour B. Changes in stone composition according to age and gender of patients: a multivariate epidemiological approach. Urol Res. 2004;32:241-7.
5. Moses R, Pais VM Jr, Ursiny M, Prien EL Jr, Miller N, Eisner BH. Changes in stone composition over two decades: evaluation of over 10,000 stone analyses. Urolithiasis. 2015;43:135-9.
6. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. Eur Urol. 2016;69:468-74.
7. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62:160-5.
8. Zeng Q, He Y. Age-specific prevalence of kidney stones in Chinese urban inhabitants. Urolithiasis. 2013;41:91-3.
9. Ye Z, Zeng G, Huan Y, Li J, Tang K, Wang G, et al. The Status and Characteristics of Urinary Stone Composition in China. BJU Int. 2019. [Epub ahead of print]
10. Edvardsson VO, Indridason OS, Haraldsson G, Kjartansson O, Palsson R. Temporal trends in the incidence of kidney stone disease. Kidney Int. 2013;83:146-52. Erratum in: Kidney Int. 2013;83:972.
11. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int. 2003;63:1817-23.
12. Indridason OS, Birgisson S, Edvardsson VO, Sigvaldason H, Sigfusson N, Palsson R. Epidemiology of kidney stones in Iceland: a population-based study. Scand J Urol Nephrol. 2006;40:215-20.
13. Wu W, Yang B, Ou L, Liang Y, Wan S, Li S, et al. Urinary stone analysis on 12,846 patients: a report from a single center in China. Urolithiasis. 2014;42:39-43.
14. Yang X, Zhang C, Qi S, Zhang Z, Shi Q, Liu C, et al. Multivariate Analyses of Urinary Calculi Composition: A 13-Year Single-Center Study. J Clin Lab Anal. 2016;30:873-9.
15. Zeng G, Mai Z, Xia S, Wang Z, Zhang K, Wang L, et al. Prevalence of kidney stones in China: an ultrasonography based cross-sectional study. BJU Int. 2017;120:109-16.
16. Das P, Gupta G, Velu V, Awasthi R, Dua K, Malipeddi H. Formation of struvite urinary stones and approaches towards the inhibition-A review. Biomed Pharmacother. 2017;96:361-70.

17. Dessombz A, Letavernier E, Haymann JP, Bazin D, Daudon M. Calcium phosphate stone morphology can reliably predict distal renal tubular acidosis. J Urol. 2015;193:1564-9.
18. Goldfarb DS. A woman with recurrent calcium phosphate kidney stones. Clin J Am Soc Nephrol. 2012;7:1172-8.
19. Cicerello E. Uric acid nephrolithiasis: An update. Urologia. 2018;85:93-8.
20. Bobulescu IA, Dubree M, Zhang J, McLeroy P, Moe OW. Effect of renal lipid accumulation on proximal tubule Na+/H+ exchange and ammonium secretion. Am J Physiol Renal Physiol. 2008;294:F1315-22.
21. Prochaska M, Taylor EN, Curhan G. Menopause and Risk of Kidney Stones. J Urol. 2018;200:823-8.
22. Zhao Z, Mai Z, Ou L, Duan X, Zeng G. Serum estradiol and testosterone levels in kidney stones disease with and without calcium oxalate components in naturally postmenopausal women. PLoS One. 2013;8:e75513.
23. Heller HJ, Sakhaee K, Moe OW, Pak CY. Etiological role of estrogen status in renal stone formation. J Urol. 2002;168:1923-7.
24. Spivacow FR, Negri AL, del Valle EE, Calviño I, Fradinger E, Zanchetta JR. Metabolic risk factors in children with kidney stone disease. Pediatr Nephrol. 2008;23:1129-33.
25. Yang D, Tiselius HG, Lan C, Chen D, Chen K, Ou L, et al. Metabolic disturbances in Chinese children with urolithiasis: a single center report. Urolithiasis. 2017;45:285-90.
26. Sun X, Shen L, Cong X, Zhu H, Lv J, He L. Infrared spectroscopic analysis of urinary stones (including stones induced by melamine-contaminated milk powder) in 189 Chinese children. J Pediatr Surg. 2011;46:723-8.
27. Huang J, Tuerxun A, Tusong H, Batuer A, Tiselius HG, Zhao Z, et al. Composition of urinary tract stones formed by children in two populations in the Uyghur region of China. J Chin Med Assoc. 2018;81:949-54.
28. Skolarikos A, Straub M, Knoll T, Sarica K, Seitz C, Petřík A, et al. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. Eur Urol. 2015;67:750-63.
29. Guan N, Fan Q, Ding J, Zhao Y, Lu J, Ai Y, et al. Melamine-contaminated powdered formula and urolithiasis in young children. N Engl J Med. 2009;360:1067-74.
30. Chen JS. A worldwide food safety concern in 2008--melamine-contaminated infant formula in China caused urinary tract stone in 290,000 children in China. Chin Med J (Engl). 2009;122:243-4.

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SUPPLEMENTARY TABLES

Supplementary Table 1 - Characteristics of patients with or without stone conversions in two episodes.

Variables	Total number N=118	Conversion N=43	No conversion N=75	P-value
Gender				
Male	68 (57.6%)	22 (51.2%)	46 (61.3%)	0.282
Female	50 (42.4%)	21 (48.8%)	29 (38.7%)	
Age (year, mean±SD)	47.3±14.7	46.7±15.5	47.7±14.2	0.617
Prior procedure (first of the two episodes)				
Ureteroscopy	56 (47.5%)	20 (46.5%)	36 (48.0%)	0.876
PCNL	62 (52.5%)	23 (53.5%)	39 (52.0%)	
Compositions (first of the two episodes)				
Calcium oxalate	61 (51.7%)	17 (39.5%)	44 (58.7%)	0.004
Infectious stone	24 (20.3%)	10 (23.2%)	14 (18.7%)	0.551
Calcium phosphate	13 (11.0%)	11 (25.6%)	2 (2.7%)	<0.001
Uric acid	14 (11.9%)	3 (7.0%)	11 (14.7%)	0.214
Cystine	3 (2.5%)	1 (2.3%)	2 (2.7%)	/
2.8-Dihydroxyadenine	1 (0.8%)	0	1 (1.3%)	/
Brushite	2 (1.7%)	1 (2.3%)	1 (1.3%)	/

Supplementary Table 2 - Multivariate analysis of the predictors for stone composition conversion.

Variables	Univariate		Multivariate	
	Odds Ratio (95% Confidence Interval)	p-value	Odds Ratio (95% Confidence Interval)	p-value
Gender				
Male	1		1	
Female	1.514 (0.710-3.229)	0.283	1.205 (0.526-2.760)	0.659
Age (year)				
<40	1		1	
40-70	0.690 (0.294-1.614)	0.392	0.651 (0.256-1.654)	0.367
>70	0.436 (0.041-4.689)	0.493	0.642 (0.055-7.498)	0.724
Prior procedure (first of the two episodes)				
Ureteroscopy	1		1	
PCNL	0.803 (0.379-1.701)	0.566	1.081 (0.387-3.014)	0.882
Compositions (first of the two episodes)				
Calcium oxalate	1		1	
Infectious stone	1.849 (0.690-4.955)	0.222	1.629 (0.518-5.121)	0.404
Calcium phosphate	14.235 (2.853-71.020)	0.001	14.178 (2.655-75.702)	0.002
Uric acid	0.706 (0.175-2.845)	0.624	0.708 (0.173-2.901)	0.631
Cystine	1.294 (0.110-15.221)	0.838	1.282 (0.102-16.096)	0.847
2.8-Dihydroxyadenine	0.000	1.000	0.000	1.000
Brushite	2.588 (0.153-43.760)	0.510	2.327 (0.129-41.841)	0.567

EDITORIAL COMMENT

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Editorial Comment: Upper urinary tract stone compositions: the role of age and gender

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Kidney stones prevalence is increasing worldwide, leading to a higher number of patients requiring medical treatment (clinical or surgical approaches) (1, 2). It has important impact on social and economic life of people suffering from urinary stones, bringing significant financial costs and becoming a relevant problem to healthcare managers. Understanding kidney stones etiology (and composition), its specific risk factors and how to prevent its formation, growth, and complications is essential to a good medical practice.

In this retrospective study including more than 1,500 stone analysis, authors have shown the influence of gender and age on stone composition. Men presented with more CaOx and UA stones, whereas the prevalence of infection and CaP stones was higher in women (3). Regarding age, prevalence of UA stones increased with aging while prevalence of infection stones decreased in both genders. Lieske et al. in a study with 43,545 stone analysis have already linked gender and age to stone composition. While women have presented with a higher prevalence of hydroxyapatite and struvite stones, men have presented with a higher prevalence of calcium oxalate and uric acid stones. Aging was also associated with a higher prevalence of uric acid stones (4). Others two studies, one from Israel and another from Turkey have also found similar outcomes (5, 6). In all studies CaOx is the most common kidney stone, regardless of age and gender, however some patterns on stone composition distribution can be noted according to gender and age.

It is exciting to know that stone composition may be associated with age and gender, but we have to be careful when interpreting these data because others factors such as dietary modifications, BMI changes over time and postmenopausal alterations in women may play also important role on stone composition.

REFERENCES

1. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62:160-5.
2. Marchini GS, Mello MF, Levy R, Vicentini FC, Torricelli FC, Eluf-Neto J, et al. Contemporary Trends of Inpatient Surgical Management of Stone Disease: National Analysis in an Economic Growth Scenario. J Endourol. 2015;29:956-62.
3. Wang S, Zhang Y, Zhang X, Tang Y, Li J. Upper urinary tract stone compositions: the role of age and gender. Int Braz J Urol. 2020;46:70-80.
4. Lieske JC, Rule AD, Krambeck AE, Williams JC, Bergstralh EJ, Mehta RA, et al. Stone composition as a function of age and sex. Clin J Am Soc Nephrol. 2014;9:2141-6.
5. Usman KD, Golan S, Abdin T, Livne PM, Pode D, Duvdevani M, et al. Urinary stone composition in Israel: current status and variation with age and sex--a bicenter study. J Endourol. 2013;27:1539-42.
6. Karabacak OR, Dilli A, Saltaş H, Yalçınkaya F, Yörükoşu A, Sertçelik MN. Stone compositions in Turkey: an analysis according to gender and region. Urology. 2013;82:532-7.

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Dorsal oral mucosa graft in combination with ventral penile flap as an alternative to repair obliterative stenosis of the anterior urethra in a single surgical time

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ABSTRACT

Purpose: Obliterative urethral stenosis is a type of urethral lesion that compromises the whole corpus spongiosum´s circumference. We present our experience in resolving complex long segment urethral obliteration in a single procedure using a combination of dorsal onlay oral mucosa graft (OMG) and ventral fasciocutaneous penile skin flap.
Materials and methods: A prospectively maintained database was reviewed, which included data of men presenting long, obliterative strictures. Patients were excluded if they were lost to follow-up before one year. Failure was defined as need for further urethral instrumentation.
The surgical technique used consisted on the fixation of OMG to the tunica albuginea of the corpus cavernosum, thus creating a new urethral plate. Penile or foreskin flaps were employed to complete the ventral aspect. Postoperative follow-up was done with a voiding cystourethrography at week 3.
Results: A total of 21 patients were included with a median age of 49 years. Mean follow-up was 25 months. Failure was found for 3 patients (2 of them needing dilations and only one required a new urethral reconstruction).
Conclusion: Single stage combination of dorsal OMG with ventral fasciocutaneous penile flap showed good results for selected patients affected with obliterative urethral stenosis.

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INTRODUCTION

The obliterative stenosis (OS) of a urethral segment is a type of urethral lesion that compromises the whole circumference of the corpus spongiosum, therefore leaving sparse urethral plate and a hostile ground for a comfortable urethroplasty.

Most urethral strictures can be solved in a single intervention using either grafts, flaps, or resection and primary anastomosis (1, 2). Nevertheless, when the damaged urethral plate segment is long and involves its whole circumference, these resources fall short and traditionally a two-staged urethroplasty following the Johanson principles is usually advised (3). This technique not only leaves patients with an hypospadic urethra for at least 6 months, but also renders the possibility of needing not only a second intervention, but often a third or more.

The use of dorsal oral mucosa graft (OMG) in combination with ventral penile fasciocutaneous flap to address obliterative stenosis of the anterior urethra in a single stage has already been described, and success outcomes as high as 83.3% have been reported (4, 5). Nevertheless, the reports on this technique consist on series of a short number of patients, and new reports with larger cohorts are in need to further validate this approach as an option for treating OS of the anterior urethra.

The following paper's objective is to present the experience of a single Latin American center with high reconstructive surgical volume in resolving complex long segment urethral obliteration bt a single procedure using a combination of dorsal onlay OMG and ventral fasciocutaneous penile skin flap.

MATERIALS AND METHODS

A prospectively maintained database was reviewed which included data of men presenting long OS which needed a whole circumference urethral replacement. OS was defined as a lesion that resulted on a complete urethral lumen obliteration and/or less than 6Fr, as defined by Dubey, et al. (6). It is important to state that the availability of healthy penile skin is paramount for patient selection, therefore patients with lichen sclerosus were not candidates for this procedure. Men were also excluded if they did not present a minimum follow-up of 12 months.

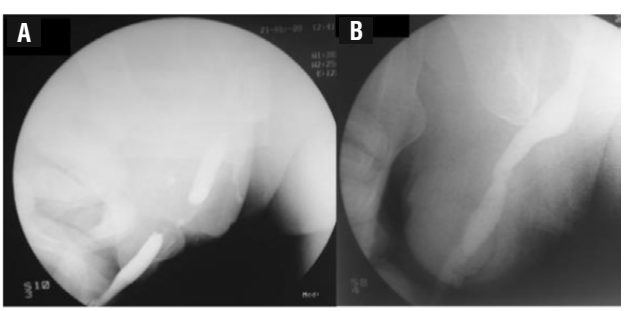
A descriptive informed consent was handed during the preoperatory evaluation.

Preoperative variables measured included: age, comorbid diseases, smoking status, etiology of the stricture, and previous urethral treatments performed.

Intra-operative variables measured included: location and length of stricture, size of graft (which, as it was used to create the urethral plate where the obliterated segment laid, is a direct indicator of the obliterated segment's length) and flap used, length of urethra repaired, and total surgical time. Comorbid conditions were measured using the Age adjusted Charlson Comorbidity Index (ACCI).

Patients were evaluated before surgery on the outpatient clinic with a combination of retrograde/voiding cystourethrography (VCUG) (Figure-1a), and flexible urethrocystoscopy, which were used to estimate the extent of the damaged urethra. Urine culture was obtained (either by spontaneous micturition or by suprapubic tube (SPT) replacement) previous to surgery to determine the need for antibiotic prophylaxis. A thorough physical examination was performed, where a careful evaluation of the penile skin quality was paramount.

Figure 1 – a) An initial CUG is performed revealing signs of long segment urethral obliteration. b) Twenty-one days after the procedure is carried out, a voiding CUG is ordered.



The operations were carried out on a single center. Urethral catheter was removed on postoperative day 21, and an immediate VCUG was performed (Figure 1b). Subsequent follow-up was carried out with uroflowmetry and clinical examination.

Treatment was considered as having failed if the patient had to undergo an additional procedure (either dilations, endoscopic procedure, or a second urethroplasty). Need for reevaluation (i.e flexible urethroscopy) was considered for patients with obstructive symptoms, recurring urinary tract infections or a maximum flow (Qmax) of less than 15mL/sec. If a relapsed stenosis was found to be the cause, the patient was advised to undergo a new manipulation, and therefore was considered as failure. Other occurring postoperative complications that didn't qualify as failure were also assessed.

Continuous and categorical variables are expressed as their median and range (r) and absolute value and percentage (%), respectively. Relapse free survival is calculated using Kaplan Meier method informed wit 95% confidence interval (95CI). The software used was SPSS 22.0(™)

SURGICAL TECHNIQUE

On the operating room, patients that have damage limited to the penile urethra re situated in dorsal decubitus. If the stricture extended also to the bulbar urethra, patients are accommodated in lithotomy position after the penile urethra is addressed. Careful care of the decubitus to avoid excessive pressure on the calves is fundamental. Pneumatic compression pumps are used to reduce risk of deep vein thrombosis.

An initial flexible urethroscopy is performed to locate the distal tip of the stricture. If it is situated on the distal penile urethra, and a circular fasciocutaneous flap is planned, a subcoronal incision and penile degloving is used to approach it. If the stricture is located on the proximal penile urethra, a longitudinal fasciocutaneous flap is performed, and a ventral longitudinal incision is made proximal to the site of disease (Figure-2a) which is located by urethroscopy (using the white light as aid). The most damaged and unsalvageable tissue is resected, the defect measured (Figures-2 b and c), and the incision extended until healthy urethral tissue is found. Another flexible urethroscopy is performed to ensure that the urethra proximal to the incised segment is of good caliber. A percutaneous 14Fr SPT is placed under cystoscopic guidance.

An initial 5-7cm OMG is harvested (tongue mucosa can also be used if cheek mucosa is not available for harvest) and fixed to the tunica albuginea of the corpus cavernosum using a 5-0 polyglactin suture to replace the absent urethral plate (Figure-3a). If the extent of the damaged urethra is too long, a second graft can also be harvested. A circular 10-15cm foreskin flap is tailored using the McAninch technique (7). The flap is then used to complete the ventral side of the neo-urethra, and/or to complete the ventral aspect of the segments where the original urethral plate is preserved (Figures-3 b and c). Non-OS present in either end of the damaged site are also treated with the ventral flap.

aTo perform the graft-flap anastomosis, a 5-0 polyglactin suture is performed in both ends, and a running 4-0 polyglyconate suture is used to fixate the lateral aspects. It is important to state that before the final lateral side is sutured, a 14Fr silicone Foley urethral catheter is placed to serve as a tutor to the neo-urethra (Figure-3d).

The Foley catheter is then removed at postoperative day 21, and an immediate VCUG is performed. The SPT is then removed if the contrast stu-

Figure 2 – a,b) Ventral incision and urethral dissection revealing severe urethral damage. c) The unsalvageable segment is resected, and the defect measured in order to objectify the length of the graft.

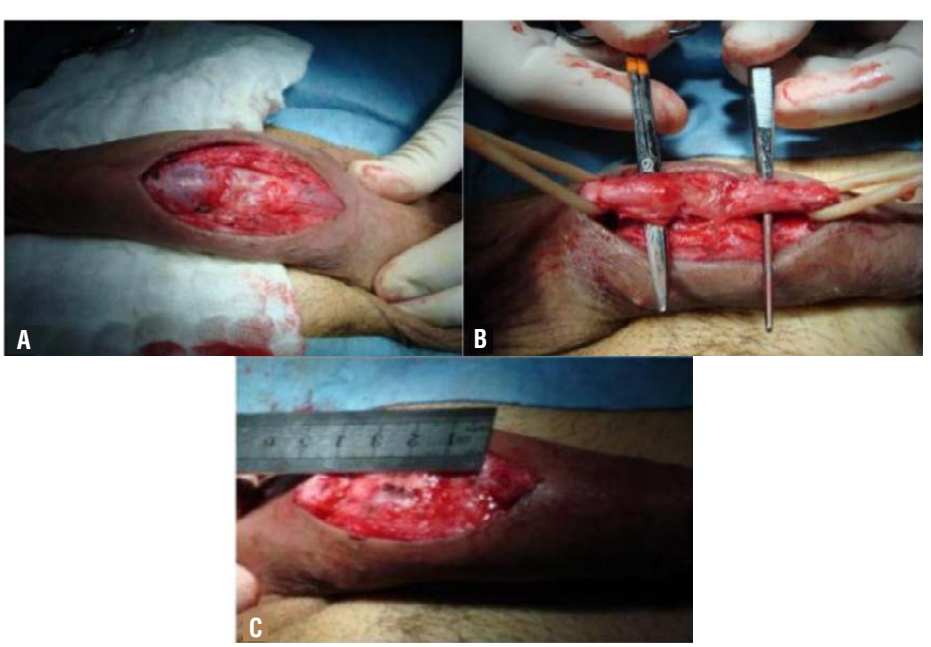
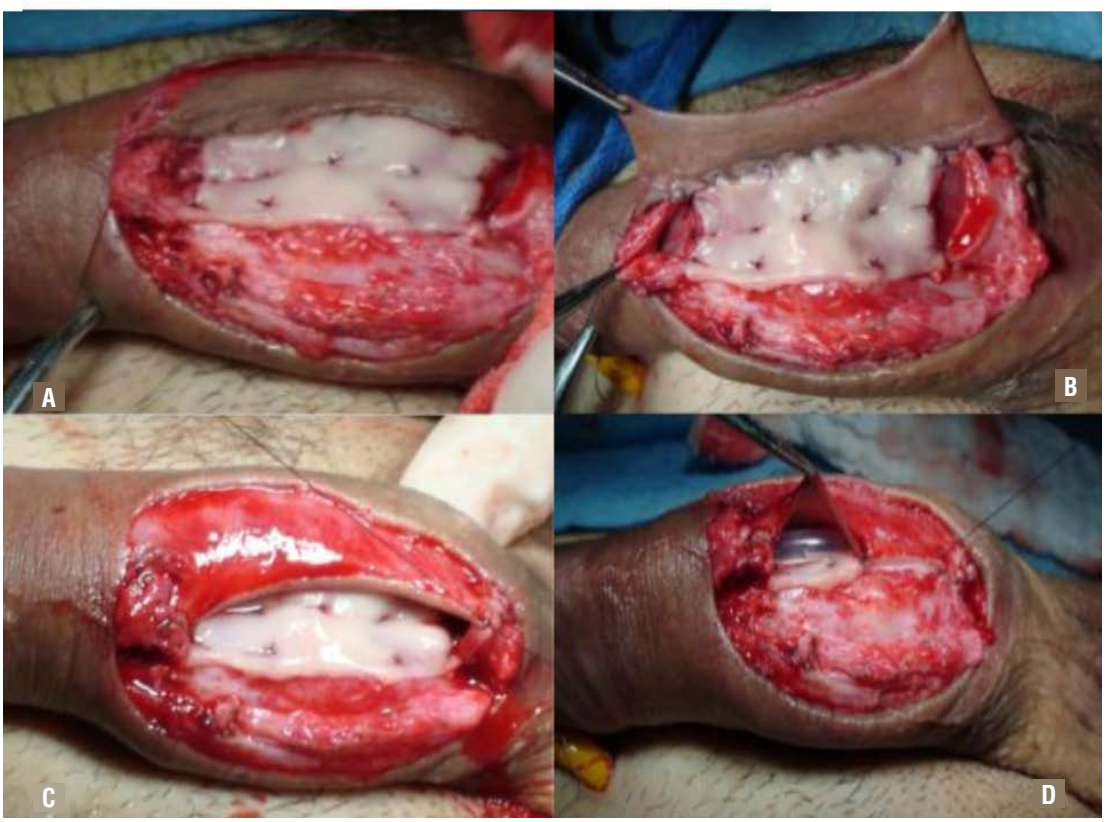


Figure 3 – a) The oral mucosa graft is harvested and fixed to the tunica albuginea of the corpus cavernosum serving as urethral plate for the resected segment. b,c) In this case, a longitudinal fasciocutaneous flap is tailored and sutured to serve as the ventral urethral aspect. d) A 14Fr silicone Foley catheter is placed prior to completion of the last suture.



dy is satisfying. If contrast extravasation is evident, the SPT is left in place for another week, and a new VCUG is scheduled. The patient is followed every 4 months in the first year using physical examination, interview, uroflowmetry and urine culture. Every 6 months in the second year, and then annually.

RESULTS

Twenty-seven men underwent the procedure between September 2003 and October 2015. Six of them were not included due to discontinued follow-up. Treatment success was achieved in 18 men (85.71%). Analyzing the population that were considered as having failed, one of them required consecutive dilations, another required a single endoscopic urethrotomy, and only one required surgical evaluation, ending up with a permanent perineal urethrostomy.

Median age at time of intervention was 49 years old. Distribution of stricture etiology is described on Table-1. Twelve participants had undergone previous treatments (Table-2). It is important to add that of the three patients that had undergone previous

Table 1 - Etiology of the stenosis of the 21 patients included in the study.

Etiology	n
Urethral catheter related injury	6
Infection related	1
Secondary to urological procedure	6
Trauma	5
Hipospadias	1
Unknown	2

Table 2 - Previous procedures underwent by patients prior to combination urethroplasty.

Endoscopic urethrotomy	5
Dilations	4
Urethroplasty	3
No previous urologic procedure	9

urethroplasties, two of them have had an urethral stent placed and had to face a reconstructive surgery to extract it due to failure (one had a two-staged repair and the other, a tubularized scrotal skin flap), the last one had a previous surgery for hypospadias. Most men (67%) presented stenosis limited to the penile urethra. Within the remaining, one man presented the stricture limited to the bulbar urethra, and 6 presented the stenosis involving both segments.

Only one patient presented history of smoking. Median of ACCI was 0 (with only 4 patients presenting an ACCI of ≥4).

Median length of the urethral stricture was 6cm (2.5-15cm), and median length of neourethra was 4cm (2.5-15cm). This is equivalent as stating that the median length of the obliterated segment was 4cm. Median surgical time was 135 minutes, and all patients required an average 72-hour hospital stay.

Median follow-up was 25 months (IQR 25-75% 12-112). Estimated two years relapse free survival was 93.8% (95%CI 81.8-100). It is important to add that 4 of the 6 patients excluded due to lack of a 12 month follow-up, got to a 6 month follow-up with correct postoperatory evolution and a near normal uroflowmetry. One of the remaining patients was scheduled for an endoscopic urethrotomy but failed to attend preoperative evaluation and was lost to follow-up; the last one did not comply with instructed postoperative consults and VCUG date. All of them were included in the relapse free survival estimation.

Other occurring complications that were not considered as failure are detailed on Table-3. Amongst these, a relatively high incidence of urethral fistulae were assessed (28%). But, all of these were transient, asymptomatic and managed conservatively, therefore not resulting on a treatment failure. No infectious complications that required hospital admission and/or intravenous antibiotics were reported.

Table 3 – Complications that did not meet criteria for failure (n = 21).

Perineal / scrotal hematoma	3 (14.2%)
Transient urethral fistula	6 (28.6%)
Asymptomatic bacteriuria	1 (4.8%)

DISCUSSION

Urethral reconstructive surgeries are not simple procedures, and they require a steep learning curve to achieve good results (8). Even the simplest stricture requires the expertise of a well-trained surgeon that profoundly understands the urethral anatomy. To aid in the process of learning how to deal with different surgical scenarios, many 'principles' have been established. One of these is the Johanson principle (3), that establishes a procedure based on a marsupialization of the strictured urethra, followed by a second surgical stage approximately 4 to 6 months after the first repair has settled. This approach, even though effective, has several down points, such as the fact that the patient has to wait at least 4 months, to be able to face the second procedure. In their cohort, Elliot et al. have shown that only 24% of the patients have opted to continue to a second procedure to complete the tubulization of the urethra, and have on the other hand chosen to remain with a permanent perineal meatus (9). The requirement of additional procedures (ie: dilations, meatus surgical revision) between the two stages is also a reality that discourages both the patient and the professional to advance to the second stage, or to offer the two-staged procedure at all (10).

Studies similar to the present one have already been carried out and also present good outcomes (4, 5). Gelman et al. obtained good results, with 10/12 without the need of additional intervention when the technique was applied to patients with stricture limited to the penile urethra. Erickson et al. also presented good outcomes with

a 65% initial success, that extends to 78%, when adding patients that had final success after a single endoscopic procedure with a median follow-up of 2.5 years. In our study we present the outcomes achieved for 21 patients, with an initial success rate of 85.71%, a global follow-up of over an year, and a median follow-up of 25 months. Thus, there is extending evidence of the feasibility of this procedure with good and durable success rate.

Using a vast population (318 patients), Kulkarni et al. (11, 12) accomplished an excellent success rate (84.9%) employing a single-stage augmentation urethroplasty using OMG through a perineal incision to repair long-segment urethral stenosis. This technique requires the use of at least two OMGs fixed in tandem (one fixed opposite to the penile urethra, and the other fixed opposite the bulbar urethra). Even though this approach requires an acceptable remnant urethral plate, it was used in 49 patients with OS. The authors report poorer results comparing these patients with those with wide urethral plate (84.9% vs. 57.1%). Dubey et al. described that patients with an affected urethra resulting on a <6Fr lumen should be replaced rather than augmented (6). That way, we believe that the Kulkarni technique is an excellent option to approach a large segment urethral stricture with acceptable remnant urethral plate. Nevertheless, evidence suggests that better results can be achieved if a substitution treatment is installed for those patients presenting an obliterative, or lower than 6Fr stricture (6).

Other techniques for approaching this disease have been described, such as the tubularized flap (13). Even though it did not show promising results when it was first described, recent evidence suggests that with further workup and proficiency of this technique, acceptable outcomes can be achieved (14). Xue et al. have improved the outcomes achieved with the tubularized flap by suturing the longitudinal edges to the tunica albuginea of the corpus cavernosum with a distance of 0.5cm between the edges. In this way, if the learning curve of this procedure is carried out, it can also serve as a valid option, especially for patients with no availability of oral mucosa to harvest.

In our opinion, not every patient is a good candidate for this approach as the availability of healthy penile skin, as well as the motivation and overall health status are crucial factors for achieving success.

Important details of the procedure must be highlighted. As we stated on the description of the surgical technique, a change of positioning was made for those patients that had to undergo repair of both the penile and bulbar urethra, and in that way reducing the time of lithotomy position. This position, although useful, is related to a range of postoperative complications such as prolonged leg pain, compartimental syndrome, or even severe acute renal failure with requirement of hemodialysis secondary to rhabdomyolysis (15, 16), and its occurrence is directly associated with the time spent on said decubitus. No position related complications were assessed in our study. However, we did register a relatively high incidence of urethral fistula (28%), but it is important to declare that all of them were successfully treated conservatively (transitory urinary diversion) and did not result in treatment failure at one year follow-up, which is in consonance with recently reported evidence (17).

The results shown in the present study were obtained on 21 men. The short cohort of patients studied are not sufficient to validate this technique as a standard treatment for OS, but we believe that the results we present (in addition to other favorable results obtained in other case series reported (4, 5)) are encouraging enough to promote this technique as a reasonable approach. Still, prospective randomized controlled data would be the ideal evidence for further validation.

Other limitations we must state is the lack of assessment of change in sexual function and aesthetic acceptance.

We consider our report as a novel task. There are few published papers about this issue (none of them focused on South American population), and all of them comprised of case-series.

In conclusion, by showing our experience with handling complex OS with a single stage combination of dorsal OMG with ventral fasciocutaneous penile flap, we show that good results can be achieved for selected patients affected with this rare, but very challenging disease.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Jezior JR, Schlossberg SM. Excision and primary anastomosis for anterior urethral stricture. Urol Clin North Am. 2002;29:373-80.
2. Levy ME, Elliott SP. Graft Use in Bulbar Urethroplasty. Urol Clin North Am. 2017;44:39-47.
3. Johanson B. The reconstruction in stenosis of the male urethra. Z Urol. 1953;46:361-75.
4. Erickson BA, Breyer BN, McAninch JW. Single-stage segmental urethral replacement using combined ventral onlay fasciocutaneous flap with dorsal onlay buccal grafting for long segment strictures. BJU Int. 2012;109:1392-6.
5. Gelman J, Sohn W. 1-stage repair of obliterative distal urethral strictures with buccal graft urethral plate reconstruction and simultaneous onlay penile skin flap. J Urol. 2011;186:935-8.
6. Dubey D, Sehgal A, Srivastava A, Mandhani A, Kapoor R, Kumar A. Buccal mucosal urethroplasty for balanitis xerotica obliterans related urethral strictures: the outcome of 1 and 2-stage techniques. J Urol. 2005;173:463-6.
7. Buckley J, McAninch J. Distal penile circular fasciocutaneous flap for complex anterior urethral strictures. BJU Int. 2007;100:221-31.
8. Fossati N, Barbagli G, Larcher A, Dell'Oglio P, Sansalone S, Lughezzani G, et al. The Surgical Learning Curve for One-stage Anterior Urethroplasty: A Prospective Single-surgeon Study. Eur Urol. 2016;69:686-90.
9. Elliott SP, Eisenberg ML, McAninch JW. First-stage urethroplasty: utility in the modern era. Urology. 2008;71:889-92.
10. Andrich DE, Greenwell TJ, Mundy AR. The problems of penile urethroplasty with particular reference to 2-stage reconstructions. J Urol. 2003;170:87-9.
11. Kulkarni S, Kulkarni J, Surana S, Joshi PM. Management of Panurethral Stricture. Urol Clin North Am. 2017;44:67-75. Erratum in: Urol Clin North Am. 2017;44:xix.
12. Kulkarni SB, Joshi PM, Venkatesan K. Management of panurethral stricture disease in India. J Urol. 2012;188:824-30.
13. McAninch JW, Morey AF. Penile circular fasciocutaneous skin flap in 1-stage reconstruction of complex anterior urethral strictures. J Urol. 1998;159:1209-13.
14. Xue JD, Xie H, Fu Q, Feng C, Guo H, Xu YM. Single-Staged Improved Tubularized Preputial/Penile Skin Flap Urethroplasty for Obliterated Anterior Urethral Stricture: Long-Term Results. Urol Int. 2016;96:231-7.
15. Biswas S, Gnanasekaran I, Ivatury RR, Simon R, Patel AN. Exaggerated lithotomy position-related rhabdomyolysis. Am Surg. 1997;63:361-4.
16. Anema JG, Morey AF, McAninch JW, Mario LA, Wessells H. Complications related to the high lithotomy position during urethral reconstruction. J Urol. 2000;164:360-3.
17. Grossgold ET, Eswara JR, Siegel CL, Vetter J, Brandes SB. Routine Urethrography After Buccal Graft Bulbar Urethroplasty: The Impact of Initial Urethral Leak on Surgical Success. Urology. 2017;104:215-219.

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EDITORIAL COMMENT

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Editorial Comment: Dorsal oral mucosa graft in combination with ventral penile flap as an alternative to repair obliterative stenosis of the anterior urethra in a single surgical time

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Recently we comment in International Brazilian Journal of Urology a important paper about the use of penile skin fap in anterior penile urethral stricture (1, 2). In this previous paper Dr. Hmida shows that penile skin ap is easy to perform, do not need urethral mobilization and had a success rate of 88%. In the present paper, Dr. Giudice in a interesting prospective study with the use in a single procedure the combination of dorsal onlay oral mucosa graft and ventral fasciocutaneous penile skin flap in in 21 patients with long segment urethral obliteration and shows that in only 14% of the patients the procedure failed. There are several options for the treatment of anterior urethral stricture (2-4). For long anterior strictures the use of grafts is very usual (4-6). The buccal mucosa grafts and fascio-cutaneous flaps are frequently used in long anterior urethral strictures (2, 7). In this paper the authors shows that the combination of the two methods (dorsal onlay oral mucosa graft and ventral fasciocutaneous penile skin flap) could be a great option in complex cases of penile urethral stricture.

REFERENCES

1. Favorito LA. Bulbar urethral stricture: penile skin flap may be a good option? Int Braz J Urol. 2019;45:871-2.
2. Hmida W, Othmen MB, Bako A, Jaidane M, Mosbah F. Penile skin flap: a versatile substitute for anterior urethral stricture. Int Braz J Urol. 2019;45:1057-63.
3. Giudice CR, Becher E, Olivares AM, Tobía I, Favre GA. Dorsal oral mucosa graft in combination with ventral penile flap as an alternative to repair obliterative stenosis of the anterior urethra in a single surgical time. Int Braz J Urol. 2020;46:83-9.
4. Prakash G, Singh BP, Sinha RJ, Jhanwar A, Sankhwar S. Is circumferential urethral mobilisation an overdo? A prospective outcome analysis of dorsal onlay and dorso - lateral onlay BMGU for anterior urethral strictures. Int Braz J Urol. 2018;44:323-9.
5. Favorito LA, Conte PP, Sobrinho UG, Martins RG, Accioly T. Double inlay plus ventral onlay buccal mucosa graft for simultaneous penile and bulbar urethral stricture. Int Braz J Urol. 2018;44:838-9.
6. Alsagheer GA, Fathi A, Abdel-Kader MS, Hasan AM, Mohamed O, Mahmoud O, et al. Management of long segment anterior urethral stricture (≥ 8cm) using buccal mucosal (BM) graft and penile skin (PS) flap: outcome and predictors of failure. Int Braz J Urol. 2018;44:163-71.
7. Barbagli G, Palminteri E, Guazzoni G, Montorsi F, Turini D, Lazzeri M. Bulbar urethroplasty using buccal mucosa grafts placed on the ventral, dorsal or lateral surface of the urethra: are results affected by the surgical technique? J Urol. 2005;174:955-7. discussion 957-8.

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Diagnostic accuracy of contrast-enhanced ultrasound for detecting bland thrombus from inferior vena cava tumor thrombus in patients with renal cell carcinoma

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ABSTRACT

Purpose: To evaluate the role of contrast-enhanced ultrasound (CEUS) in differentiating bland thrombus from tumor thrombus of the inferior vena cava (IVC) in patients with renal cell carcinoma (RCC).

Materials and Methods: We retrospectively investigated 30 consecutive patients who underwent robot-assisted radical nephrectomy with IVC thrombectomy and had pathologically confirmed RCC. All patients underwent US and CEUS examination. Two offline readers observed and recorded thrombus imaging information and enhancement patterns. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value for bland thrombus were assessed.

Results: Of the 30 patients, no adverse events occurred during administration of the contrast agent. Early enhancement of the mass within the IVC lumen on CEUS was an indicator of tumor thrombus. Bland thrombus showed no intraluminal flow on CEUS. There were eight (26.7%) patients with bland thrombus, including three level II, two level III, and three level IV. There were three cases with cephalic bland thrombus and five cases with caudal bland thrombus. Three caudal bland thrombi extended to the iliac vein and underwent surgical IVC interruption. Based on no intraluminal flow, for bland thrombus, CEUS had 87.5% sensitivity, 100% specificity, 96.7% accuracy, 100% positive predictive value and 95.6% negative predictive value.

Conclusion: Our study demonstrates the potential of CEUS in the differentiation of bland and tumor thrombus of the IVC in patients with RCC. Since CEUS is an effective, inexpensive, and non-invasive method, it could be a reliable tool in the evaluation of IVC thrombus in patients with RCC.

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INTRODUCTION

Approximately 4-10% of cases of renal cell carcinoma (RCC) are associated with inferior vena cava (IVC) tumor thrombus (1, 2). Embolization of tumor and bland thrombus is a potential fatal complication for patients undergoing radical nephrectomy and tumor thrombectomy (3). Several surgical strategies have been proposed to prevent the dissemination of bland thrombus after surgery, including placement of a filter in the IVC, and IVC ligation and segmental resection (4). Bland thrombus is associated with adverse survival outcome in patients treated surgically for RCC with IVC tumor

thrombus (5). Therefore, discrimination of bland and tumor thrombus is of clinical significance for determining the therapeutic approach and predicting survival.

Contrast-enhanced ultrasound (CEUS) is emerging as a valuable imaging modality that complements and enhances conventional vascular US imaging in clinical and scientific settings. US contrast agents are gas-filled microbubbles that are injected into the bloodstream and serve as strict intravascular reflectors of ultrasound waves, providing real-time assessment of the dynamic temporal and spatial heterogeneity of the macro--and micro-vascular perfusion (6). Contrast-specific image processing techniques based on the nonlinear scattering properties from microbubbles allow enhancement of vascular structures and quantification of tissue perfusion. Therefore, CEUS is effective in evaluating tissue vascularity and has been widely used in different organs, lesions and vascular diseases in recent years (7-11). Previous reports have concluded that CEUS is an excellent method for differentiation of malignant from benign portal vein thrombosis in hepatocellular carcinoma (12-14).

To the best of our knowledge, the value of CEUS has not been studied for differentiation between bland and tumor thrombus of the IVC in patients with RCC. The purpose of this study was to investigate the value of CEUS imaging in distinguishing bland thrombus from tumor thrombus in the IVC in patients with RCC.

MATERIALS AND METHODS

Patients

This study was approved by the Ethics Committee of the PLA General Hospital, China and written informed consent was obtained from each patient. The study included 30 consecutive patients who underwent robot-assisted radical nephrectomy with IVC thrombectomy and had pathologically confirmed RCC between October 2017 and August 2018. IVC thrombus level was categorized as previously described (1). Patients with level 0 thrombus who did not undergo IVC resection were excluded from the study. A total of 30 patients with level I-IV thrombus formed the analytical cohort for this study. Patient characteristics (age, gender, body mass index, clinical stage, thrombus classification, and thrombus length) were collected and analyzed (Table-1).

US contrast agents (UCAs)

UCAs are gas-containing microspheres with an outer shell of lipid, protein or polymer (15). With a diameter ranging from 1 to 10μm, these microbubbles are roughly the size of a red blood cell. This size allows them to pass through capillaries and be delivered to any tissue that maintains circulation, while avoiding extravascular passage (16, 17). In practice, UCAs cause a low incidence of adverse effects and are considered safe for patients with decreased renal function. These patients benefit from the fact that the UCAs are not excreted into the urine and therefore not nephrotoxic (18). UCAs are also used in the pediatric population, and in numerous other documented areas. The US Food and Drug Administration recently approved the use of Lumason™ (marketed as SonoVue™, Bracco, Milan, outside the US) for pediatric liver imaging (19).

CEUS data acquisition

Patients were advised to follow a low-residual diet the day before CEUS examination and to fast in the morning of the day of the examination. US and CEUS were performed by the same sonographer with 5 year's experiences with abdominal CEUS. Examinations were performed transabdominally with the patients in different positions. Both US and CEUS were performed with a Resona 7 (Mindary Medical Solutions, Shenzhen, China) equipped with UWN+software using an SC6-1U abdominal transducer, pulse inversion (PI) and power modulation (PM) modes at a mechanical index of 0.08. Contrast agent SonoVue® (Bracco, Milan, Italy) was used for CEUS. SonoVue® is a second--generation sulfur hexafluoride microbubble contrast agent that provides strong and continuous real-time imaging. A 1.5mL contrast agent bolus was injected through a 20-gauge cannula followed by 5mL normal saline flushing, using a three-way stopcock to ensure that no residual contrast agent was left in the intravenous catheter. Images and cine clips of the entire CEUS examination were stored digitally for offline analysis.

Table 1 - Descriptive clinicopathologic characteristics of the 30 patients with clear cell renal cell carcinoma and inferior vena cava tumor thrombus.

Characteristics	Results
Patients, n	30
Median age, yr (interquartile range)	57.6 (46.5-65.3)
Male/Female (n)	20/10
Mean body mass index, kg/m² (range)	24.6 (17.8-30.5)
Affected kidney (n)	
Left	9
Right	21
Mean tumor size, cm (range)	7.5 (3.1-15.7)
Clinical stage (n)	
T3aN0M0	3
T3bN0M0	18
T3bN0M1	5
T3cN0M1	2
T3bN0M1	2
IVC thrombus classification (n)	
Level I	10
Level II	14
Level III	3
Level IV	3
Mean IVC thrombus length cm (range)	7.7 (4.8-13.6)
Presence of bland thrombus (n)	8
Superior bland thrombus (n)	3
Caudal bland thrombus (n)	5
Surgical strategy during IVC thrombectomy	
Incision of the IVC for thrombectomy (n)	25
IVC segmental transection(n)	5

CEUS image analysis

All patients underwent US, which revealed thrombus height, length, width, boundaries, modalities, echo features and color Doppler flow imaging information. After CEUS, two off-line readers observed and recorded thrombus enhancement patterns. Both readers were skilled in urological sonography with >5 years of CEUS examination experience, and were blinded to patient final diagnoses and clinical and radiological information. If there was disagreement between the two readers, another pair of senior physicians re-evaluated the clips until a final conclusion was reached. Evaluation of the CEUS findings was conducted as follows: early enhancement of a mass within the IVC lumen on CEUS was an indicator of tumor thrombus, and IVC bland thrombus showed no intraluminal flow on CEUS.

Histological examination

Within 7 days after CEUS examination, all patients underwent robot-assisted radical nephrectomy with IVC thrombectomy. Histological diagnosis was performed according to the World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs (20). Presence of bland thrombus was defined as any noted bland thrombus within the operative report or noted in the pathology report.

Postoperative treatment and follow-up

For follow-up and surveillance of the patients, US, computed tomography (CT) and magnetic resonance imaging (MRI) scans of the chest, abdomen and pelvis were performed every 6 months.

RESULTS

Technical success for CEUS was obtained in all the patients. Every CEUS examination was of sufficient quality to enable analysis and no relevant motion artefacts were encountered. No adverse events occurred during administration of the contrast agent. The information from surgery and pathology confirmed the diagnosis of clear cell RCC in all the 30 patients who underwent nephrectomy with IVC thrombectomy. The thrombus level was I in 10 patients (33.3%), II in 14 patients (46.7%), III in three patients (10%), and IV in three patients (10%).

We used robotic techniques that depend on the level of venous thrombus, as described previously and summarized by our department (21-23). For a thrombus inferior to the first porta hepatis (level I and part of level II), we ligated some short hepatic veins. For a thrombus between the first porta hepatis and second porta hepatis (level II), we mobilized the right lobe of the liver from the IVC by ligating additional short hepatic veins. For a thrombus near or above the second porta hepatis but below the diaphragm (level III), we mobilized the right and left lobes of the liver to obtain high proximal control of the suprahepatic and infradiaphragmatic IVC, and simultaneously clamped the first porta hepatis. For a thrombus above the diaphragm and in the right atrium (level IV), we established cardiopulmonary bypass (CPB), and performed the thoracoscopy-assisted thrombectomy for the intra-atrial part of the thrombus under CPB. The infradiaphragmatic part was treated in a manner similar to that of level III.

Cephalic bland thrombus and short caudal bland thrombus were treated as tumor thrombus. For patients with long caudal bland thrombus associated with tumor thrombus, in which the thrombus filled the IVC lumen and where there was excellent collateral circulation, we simply ligated the IVC above and below the thrombus, and the renal vein using an Endo GIA stapler (Medtronic, Minneapolis, MN, USA) with a 45mm vascular load.

There were eight (26.7%) patients with bland thrombus, including three level II, two level III, and three level IV. There were three patients with cephalic bland thrombus (Figure-1) and five with caudal bland thrombus. Three caudal bland thrombi extended to the iliac vein (Figure-2). Enhancement pattern of the thrombi helped to distinguish bland from tumor thrombi (Figure-3). Based on 100% agreement between the two observers, there was 87.5% (7/8) agreement between CEUS and intraoperative findings in differentiating bland from tumor thrombi. Diagnosis of one case of tiny caudal bland thrombus was missed by CEUS. Based on no intraluminal flow, for bland thrombus, CEUS had 87.5% sensitivity, 100% specificity, 96.7% accuracy, 100% positive predictive value and 95.6% negative predictive value.

Five patients had the IVC interrupted by ligation below the tumor thrombus. After thrombectomy, no intraoperative IVC filter placement was performed through the cavatomy, and none of the 30 patients had a bland thrombus pulmonary embolus during or after surgery. Eight patients developed mild to severe renal dysfunction. We isolated and excised lymph nodes proximal to the IVC in 12 patients, and positive findings were observed in four cases. During the follow-up of a median of 12 months (range 10-20 months), no tumor embolus infringement of the IVC wall or positive lymph nodes or distant metastasis was found.

Figure 1 - Example case of left-sided renal tumor with a level IV IVC thrombus in a 55 years old male patient. A) CEUS scan obtained 36 s after injection of microbubbles showed heterogeneous enhancement within the thrombus involving the LRV and IVC. In situ mapping of blood flow using B mode US image of thrombus (right) with CEUS mode (left). B) CEUS scan showed no enhancement within the bland thrombus of the superior IVC in RA (arrows) and strong enhancement within the tumor thrombus of the IVC (arrows). C) Intraoperative robotic view of the bland thrombus of the superior IVC (arrow). LRV=Left renal vein, AO=Abdominal aorta, BT=bland thrombus, LI=liver, SMA=superior mesenteric artery, T=thrombus, TT=tumor thrombus, RA=right atrium.

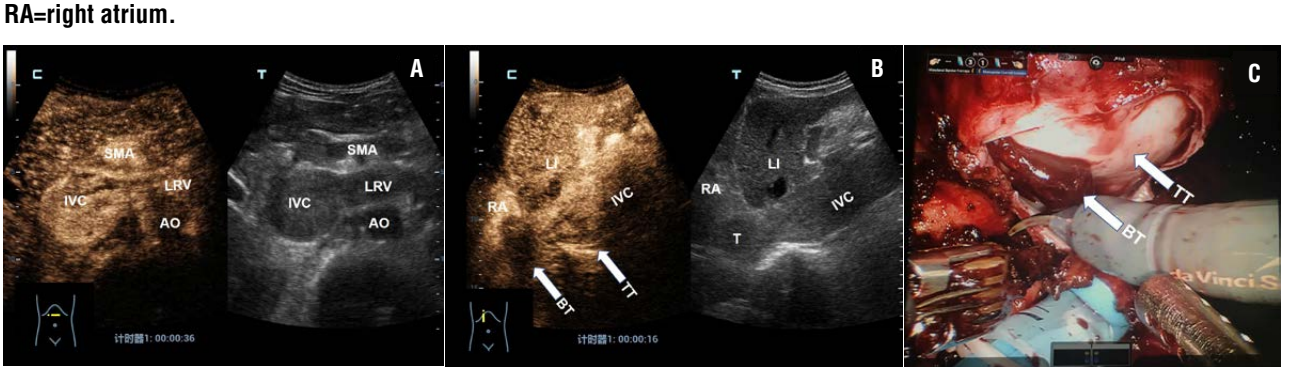


Figure 2 - Example case of right-sided renal tumor with a level III IVC thrombus in a 60-year-old male patient. A) CEUS scan showed strong enhancement within the tumor thrombus of the proximal segment of the IVC (arrows) and no enhancement within the bland thrombus of the distal segment (arrows). B) CEUS scan showed no enhancement within the bland thrombus of the distal segment of the IVC (arrows). C) CEUS scan showed no enhancement within the bland thrombus of the bilateral iliac vein.

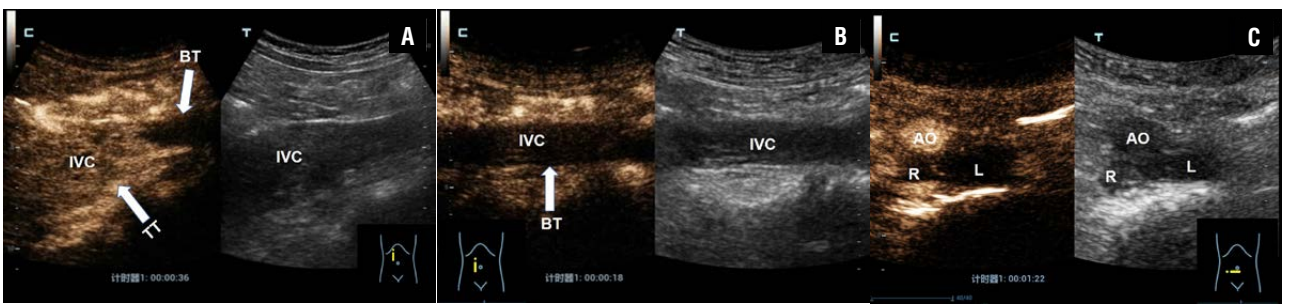
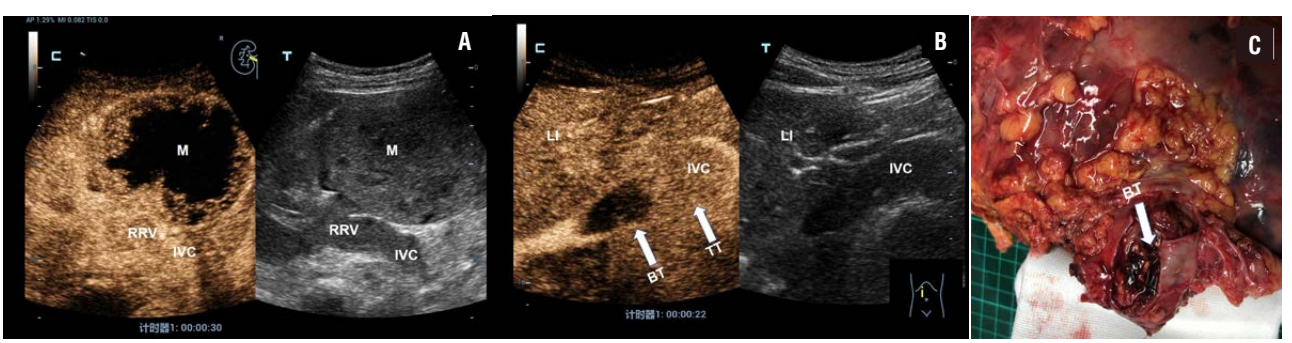


Figure 3 - Example case of right-sided renal tumor with a level II IVC thrombus in a 45-year-old female patient. A) B-mode imaging showed a mass at the mid and lower posterolateral right kidney, solid hypoechoic thrombus in RRV and IVC (right). CEUS scan showed heterogeneous enhancement in the right renal mass and homogeneous, complete enhancement of the tumor thrombus in the RRV and IVC (left). B) CEUS scan showed strong enhancement within the tumor thrombus of the distal segment of the IVC (arrows) and no enhancement within the bland thrombus of the proximal segment of the IVC (arrows). C) Postoperative gross specimens showed tumor thrombus with superior bland thrombus in the IVC.



DISCUSSION

The safety and feasibility of robot-assisted laparoscopic IVC thrombectomy have been investigated in our previous studies (21-23). We found that coexisting bland thrombus was not uncommon in RCC patients with IVC tumor thrombus. In the present study, we found eight (26.7%) patients with coexistent bland thrombus, the incidence was higher than that reported in the literature (2, 4, 5). There could be two reasons for this. First, only a small number of patients were included in our study. Second, the patients admitted to our center have complex conditions. Bland thrombus only occurred in patients with level II-IV tumor thrombus. The presence of bland thrombus associated with tumor thrombus should alert the surgical team to a possible complex and challenging surgical encounter. The surgical significance of coexisting bland thrombus has been reported (4). In our study, in three patients with cephalic bland thrombus, we suggested immediate surgery in case they progressed rapidly. For the surgical strategy, we regard the level of bland thrombus as tumor thrombus and occlude the IVC superior to the bland thrombus. Small distal bland thrombus can be removed directly, whereas most distal thrombi extend to the iliac bifurcation and cannot be removed. In the latter cases, we aim for negative margins by identifying the distal margin of the tumor thrombus and then proceeding to ligate and divide the IVC. Moreover, we perform segmental

resection of the IVC when the tumor thrombus is adherent to the vessel wall or if there is no identifiable interface between tumor and bland thrombi (22, 23). Association of bland with tumor thrombus should alert the surgical team to a potentially challenging surgical situation. About half of the patients with bland thrombus require IVC ligation or segmental resection (4, 5). Precise preoperative imaging to differentiate bland from tumor thrombus is a key step in achieving the surgical goal with minimal morbidity.

Although conventional venography remains the "gold standard" for diagnosing vein thrombosis, it is invasive and exposes patients to ionizing radiation. In clinical practice, to reliably differentiate bland from tumor thrombus, CT and MRI rely on the use of contrast media. Apart from allergic reactions, CT contrast media are associated with an increased risk of renal failure and MRI contrast agents carry a risk of nephrogenic systemic fibrosis in patients with highly impaired renal function (24, 25). RCC patients with bland or tumor thrombus in the IVC are at an especially high risk for nephrogenic systemic fibrosis, as they often suffer from impaired renal function (26). Furthermore, with recent literature reporting gadolinium deposition in the brain and other body tissues of unknown clinical significance after repeated administration of gadolinium-based contrast agents, concerns for patient safety are rising and institutional review of policies for gadolinium administration is warranted (27). UCAs are administered safely in various applications with minimal risk to patients. They are not excreted through the kidneys, and can be safely be administered to patients with renal insufficiency with no risk of contrast-related nephropathy or nephrogenic systemic fibrosis. UCAs have a low rate of anaphylactoid reactions (1:7000 patients, 0.014%), significantly lower than the rate with iodinated state-of-the-art CT agents (35-95:100.000 patients, 0.035-0.095%), but comparable to the rate of severe anaphylactoid reactions associated with gadolinium-based contrast agents at 0.001-0.01% (10).

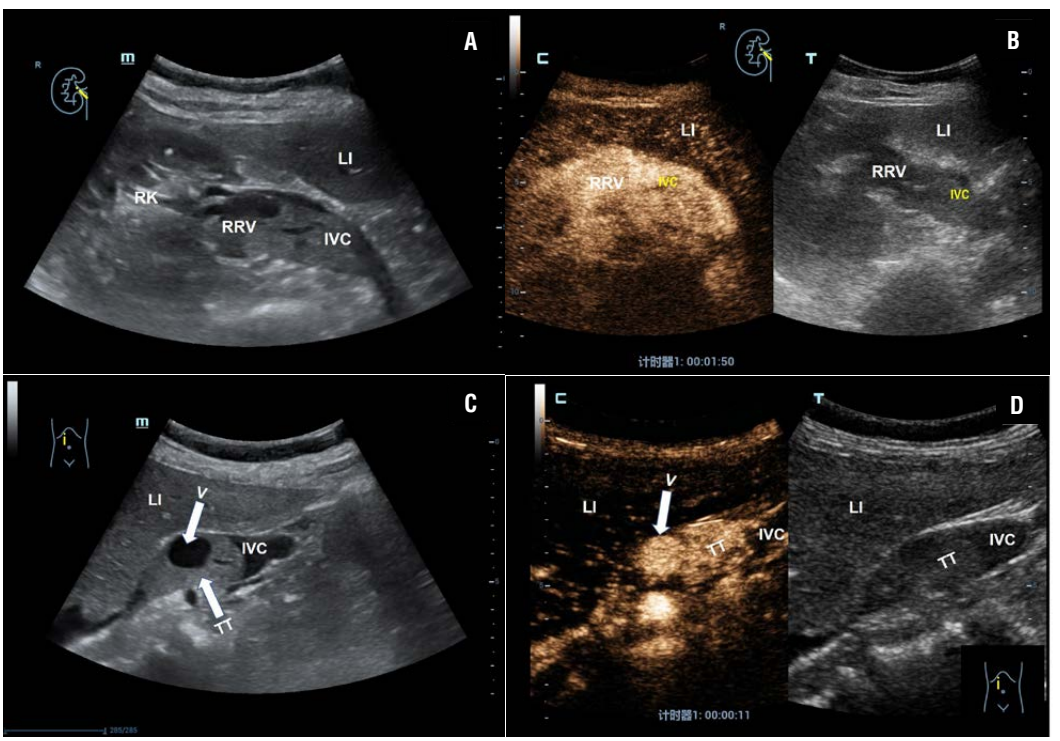
CEUS provides real-time examination of tissue enhancement. Arterial neovascularization within a tumor thrombus results in arterial enhancement, which, on real-time imaging, can be easily distinguished from venous enhancement by its timing and intermittent pulsation. CEUS has a high intrinsic sensitivity because the microbubbles produce echoes that are thousand billion times stronger than the echo from similar-sized red blood cells. This, together with the background tissue suppression using pulse inversion methods, results in high intrinsic contrast between contrast-enhanced blood and tissue (14, 28). Previous investigators have shown promising results with CEUS for discriminating malignant or benign venous thrombus in liver (29). These results were confirmed and extended in a subsequent study on a large series of patients with hepatic cirrhosis in which CEUS showed a high sensitivity (94%) and specificity (96%) in differentiating malignant versus bland portal vein thrombosis. Based on all these data, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) included the "differential diagnosis between malignant and benign portal vein thrombosis" among indications for CEUS in their updated guidelines (30).

Our study focused on identifying the individual CEUS features most helpful in differentiating bland and tumor thrombi, and showed a high sensitivity (87.5%) and specificity (100%) of CEUS. With regard to specific features, enhancement of the thrombus was the most important finding to diagnose tumor thrombus, with excellent interobserver agreement. Presence of formed vessels is another useful feature, which is detected more accurately with contrast enhancement due to the blood pool nature of the contrast agent (Figure-4). The tiny vessels in tumor thrombus can be seen on CEUS, but may be beyond the resolution threshold of conventional color Doppler ultrasound and therefore can be missed.

To the best of our knowledge, the present study is one of the first to investigate the utility of CEUS in distinguishing bland from tumor thrombus in IVC in patients with RCC.

There were two limitations to the present study. First, the retrospective single institution design and the small number of patients may have led to selection bias. Second, we did not compare CT and MRI findings due to the retrospective nature of the study and the comparison was not the purpose of this study.

Figure 4 - Example case of right-sided renal tumor with a level II IVC thrombus in a 53-year-old female patient. A) B-mode imaging showed solid hypoechoic thrombus in the RRV and IVC. B) CEUS scan showed more lasting, homogeneous, complete marked enhancement of the tumor thrombus in the RRV and IVC. There was adjacent liver washout at 1 min 50s post-injection. C) B-mode imaging showed a formed vessel in the tumor thrombus of the IVC (arrows). D) CEUS scan showed rapid and strong enhancement of the formed vessel in tumor thrombus 11s after injection of microbubbles.



CONCLUSION

CEUS has high diagnostic accuracy for the differentiation of bland from tumor thrombi of the IVC in patients with RCC. Since CEUS is an effective, inexpensive, and non-invasive method, it could be a reliable tool for evaluation of thrombus in the IVC in patients with RCC.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Blute ML, Leibovich BC, Lohse CM, Cheville JC, Zincke H. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int. 2004;94:33-41.
2. Al Otaibi M, Abou Youssif T, Alkhaldi A, Sircar K, Kassouf W, Aprikian A, et al. Renal cell carcinoma with inferior vena caval extention: impact of tumour extent on surgical outcome. BJU Int. 2009;104:1467-70.
3. Lee A. VTE in patients with cancer--diagnosis, prevention, and treatment. Thromb Res. 2008;123 Suppl 1:S50-4.

4. Ayyathurai R, Garcia-Roig M, Gorin MA, González J, Manoharan M, Kava BR, et al. Bland thrombus association with tumour thrombus in renal cell carcinoma: analysis of surgical significance and role of inferior vena caval interruption. BJU Int. 2012; 110 (11 Pt B):E449-55.
5. Hutchinson R, Rew C, Chen G, Woldu S, Krabbe LM, Meissner M, et al. The Adverse Survival Implications of Bland Thrombus in Renal Cell Carcinoma With Venous Tumor Thrombus. Urology. 2018;115:119-24.
6. Feinstein SB, Coll B, Staub D, Adam D, Schinkel AF, ten Cate FJ, et al. Contrast enhanced ultrasound imaging. J Nucl Cardiol. 2010;17:106-15.
7. Parker JM, Weller MW, Feinstein LM, Adams RJ, Main ML, Grayburn PA, et al. Safety of ultrasound contrast agents in patients with known or suspected cardiac shunts. Am J Cardiol. 2013;112:1039-45.
8. Zhang XY, Luo Y, Wen TF, Jiang L, Li C, Zhong XF, et al. Contrast-enhanced ultrasound: Improving the preoperative staging of hepatocellular carcinoma and guiding individual treatment. World J Gastroenterol. 2014;20:12628-36.
9. Piscaglia F, Nolsøe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, et al. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. Ultraschall Med. 2012;33:33-59.
10. Sidhu PS, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, et al. The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Short Version). Ultraschall Med. 2018;39:154-80.
11. Staub D, Partovi S, Imfeld S, Uthoff H, Baldi T, Aschwanden M, et al. Novel applications of contrast-enhanced ultrasound imaging in vascular medicine. Vasa. 2013;42:17-31.
12. Tarantino L, Ambrosino P, Di Minno MN. Contrast-enhanced ultrasound in differentiating malignant from benign portal vein thrombosis in hepatocellular carcinoma. World J Gastroenterol. 2015;21:9457-60.
13. Raza SA, Jang HJ, Kim TK. Differentiating malignant from benign thrombosis in hepatocellular carcinoma: contrast-enhanced ultrasound. Abdom Imaging. 2014;39:153-61.
14. Salman S. Portal vein thrombosis with contrast-enhanced ultrasound in a patient with hepatocellular carcinoma: a case study. Australas J Ultrasound Med. 2012;15:67-70.
15. Cokkinos DD, Antypa EG, Skilakaki M, Kriketou D, Tavernaraki E, Piperopoulos PN. Contrast enhanced ultrasound of the kidneys: what is it capable of? Biomed Res Int. 2013;2013:595873.
16. Quaia E, Bertolotto M, Cioffi V, Rossi A, Baratella E, Pizzolato R, et al. Comparison of contrast-enhanced sonography with unenhanced sonography and contrast-enhanced CT in the diagnosis of malignancy in complex cystic renal masses. AJR Am J Roentgenol. 2008;191:1239-49.
17. Malhi H, Grant EG, Duddalwar V. Contrast-enhanced ultrasound of the liver and kidney. Radiol Clin North Am. 2014;52:1177-90.
18. O'Neal D, Cohen T, Peterson C, Barr RG. Contrast-Enhanced Ultrasound-Guided Radiofrequency Ablation of Renal Tumors. J Kidney Cancer VHL. 2018;5:7-14.
19. Fetzer DT, Rafailidis V, Peterson C, Grant EG, Sidhu P, Barr RG. Artifacts in contrast-enhanced ultrasound: a pictorial essay. Abdom Radiol (NY). 2018;43:977-97.
20. Moch H, Humphrey P, Ulbright T, et al. WHO classification of tumours of the urinary system and male genital organ. Lyon;IARC Press, 2016.
21. Wang B, Li H, Ma X, Zhang X, Gu L, Li X, et al. Robot-assisted Laparoscopic Inferior Vena Cava Thrombectomy: Different Sides Require Different Techniques. Eur Urol. 2016;69:1112-9.
22. Wang B, Li H, Huang Q, Liu K, Fan Y, Peng C, et al. Robot-assisted Retrohepatic Inferior Vena Cava Thrombectomy: First or Second Porta Hepatis as an Important Boundary Landmark. Eur Urol. 2018;74:512-20.
23. Wang B, Huang Q, Liu K, Fan Y, Peng C, Gu L, et al. Robot-assisted Level III-IV Inferior Vena Cava Thrombectomy: Initial Series with Step-by-step Procedures and 1-yr Outcomes. Eur Urol. 2019. [Epub ahead of print]
24. Nouh MA, Inui M, Kakehi Y. Renal Cell Carcinoma with IVC Thrombi; Current Concepts and Future Perspectives. Clin Med Oncol. 2008;2:247-56.
25. Ng CS, Wood CG, Silverman PM, Tannir NM, Tamboli P, Sandler CM. Renal cell carcinoma: diagnosis, staging, and surveillance. AJR Am J Roentgenol. 2008;191:1220-32.
26. Chang A, Finelli A, Berns JS, Rosner M. Chronic kidney disease in patients with renal cell carcinoma. Adv Chronic Kidney Dis. 2014;21:91-5.
27. Malayeri AA, Brooks KM, Bryant LH, Evers R, Kumar P, Reich DS, et al. National Institutes of Health Perspective on Reports of Gadolinium Deposition in the Brain. J Am Coll Radiol. 2016;13:237-41.
28. Burns PN, Wilson SR, Simpson DH. Pulse inversion imaging of liver blood flow: improved method for characterizing focal masses with microbubble contrast. Invest Radiol. 2000;35:58-71.

29. Tarantino L, Francica G, Sordelli I, Esposito F, Giorgio A, Sorrentino P, et al. Diagnosis of benign and malignant portal vein thrombosis in cirrhotic patients with hepatocellular carcinoma: color Doppler US, contrast-enhanced US, and fine-needle biopsy. Abdom Imaging. 2006;31:537-44.

30. Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) - update 2008. Ultraschall Med. 2008;29:28-44.

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ORIGINAL ARTICLE

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The relationship of neutrophil to lymphocyte ratio with testicular cancer

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ABSTRACT

Purpose: To assess the relationship between testicular germ cell tumors (TGCT) and neutrophil to lymphocyte ratio (NLR) and to determine whether this ratio can be used as a serum tumor marker.

Material and Methods: Sixty-one patients with testicular germ cell tumors were included into the study. Patients were grouped as localized and non-localized. Histologically patients were categorized as seminoma and nonseminomatous germ cell tumors. Complete blood cell count was measured the day before surgery and at the postoperative 1st month. Preoperative and postoperative mean NLR values were compared.

Results: Thirty-six patients (59%) had seminomas and 25 patients (41%) had nonseminomatous testicular cancer. Forty-five patients (73.8%) had localized and 16 patients (26.2%) had non-localized testicular cancer. There was a statistically significant difference between preoperative and postoperative mean NLR of the localized patients (p=0.001) but no such difference was detected for non-localized patients (p=0.576). Nineteen patients with localized seminomas had normal preoperative serum tumor markers. There was a significant difference between preoperative and postoperative mean NLR in this group of patients (p=0.010). Twenty-six patients with localized tumors had preoperative increased serum tumor markers which normalized after orchiectomy. Mean NLR of these patients significantly decreased from 3.10±2.13 to 1.62±0.59 postoperatively (p=0.010).

Conclusions: NLR appears to be a useful marker for TGCT. It is successful in predicting localized and non-localized disease in early postoperative period.

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INTRODUCTION

Testicular cancer is a relatively rare malignancy which forms 1% of all male cancers but it is the most common type of malignancy in men between ages of 15 and 44 (1, 2). Histologically, 90% of testicular cancers are germ cell tumors which divided into two groups as seminomatous and non-seminomatous germ cell tumors (3). Serum tumor markers play a crucial role in diagnosis, treatment and follow-up of patients with TGCT. There are three serum tumor markers currently used for TGCT: Alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH). These markers are not very specific; AFP and HCG are increased in 50-70% and in 40-60% of patients with non-seminomatous germ cell tumors, respectively, whereas HCG elevation can be detected in only 30% of seminomas (4). LDH is a less specific marker reflecting growth rate and tumor volume, its level can be elevated in 80% of advanced seminomas and 60%

of non-seminomatous tumors (5). In clinical stage 1 TGCT, fewer patients present with elevated serum tumor markers (6). Patients whose serum tumor markers normalize after orchiectomy are clinically disease free and surveillance or adjuvant treatment can be offered depending on the risk factors for occult metastatic disease (4). Patients with clinical stage 1 disease whose serum tumor markers remains elevated after orchiectomy are categorized as clinical stage 1S. These patients should be accepted to have systemic disease and treated with chemotherapy (7). Mostly TGCT metastasize via lymphatic route to retroperitoneal lymph node, lung, liver, bone and brain are other sites of metastasis (8).

There is increasing evidence supporting that inflammation plays a critical role in different aspects of cancer such as tumor development, progression and prognosis (9). Inflammatory cells produce several mediators and cytokines that can induce or promote angiogenesis, tumor growth, invasion and metastasis (10, 11). Also, it has been hypothesized that synthesis of inflammatory cytokines can be triggered by the tumor microenvironment resulting in alterations of acute phase reactants such as serum neutrophil and lymphocyte counts (12). There are several reports investigating relationship of various cancers with markers of systemic inflammatory response such as C-reactive protein, neutrophil count, platelet count and neutrophil to lymphocyte ratio (13). It has been reported that pretreatment NLR is related with recurrence and prognosis in colorectal, gastric, kidney and bladder cancers (14-16). NLR is defined as the absolute neutrophil count divided by absolute lymphocyte count and it is an inexpensive marker that can be easily acquired from complete blood cell parameters.

In this study, we aimed to reveal the relationship between TGCT and neutrophil to lymphocyte ratio and to determine whether this ratio can be used as a serum tumor marker for TGCT.

MATERIAL AND METHODS

Data of the patients who underwent radical orchiectomy due to testicular cancer between 2014 and 2018 were analyzed retrospectively. Patients with testicular stromal tumors, infectious or inflammatory conditions, hematological disease, other malignancies, diabetes mellitus, cardiovascular diseases, end-stage renal disease, corticosteroid or B-agonist users and patients with missing data including preoperative and postoperative complete blood count, HCG, AFP, LDH and thoraco-abdominal tomography were excluded. Sixty-one patients with testicular germ cell tumor were included in the study whose preoperative and postoperative HCG, AFP, LDH and complete blood count values were available. Patients with no retroperitoneal or distant metastasis on computed tomography and no elevated serum markers following orchiectomy (stage 1A and stage 1B) were categorized as localized and patients with retroperitoneal or distant metastasis or elevated serum markers following orchiectomy (stage 1S, stage 2 and stage 3) were categorized as non-localized. Histologically patients were categorized as seminoma and non-seminomatous germ cell tumors.

Complete blood cell count was measured in the day before surgery and at the postoperative 1st month. NLR was defined as neutrophil count divided by lymphocyte count. Tumor markers were measured one week after surgery and for the patients whose marker levels declined but did not return to normal another measurement was performed 3 weeks later.

For statistical analysis, NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used. Study data were evaluated using descriptive statistical methods (mean, standard deviation, minimum, maximum, frequency and ratio). Mann Whitney U test was used for intergroup comparisons of quantitative data without normal distribution and Wilcoxon signed rank test was used for comparison of the changes seen in two paired measurements. Pearson's correlation coefficient was used to elucidate the correlation between tumor size and preoperative NLR. A p value <0.05 was considered statistically significant. Receiver operating characteristics curve analysis was performed to find cut-off levels for NLR as a predictor of localized and non-localized TGCT.

RESULTS

Mean age of the patients was 37.83±9.98 years. Thirty-six patients (59%) had seminomas and 25 patients (41%) had nonseminomatous testicular cancer. Forty-five patients (73.8%) had localized and 16 patients (26.2%) had non-localized testicular cancer. Demographic characteristics of the patients are summarized in Table-1. All of the nonseminomatous tumors were mixed germ cell tumors; 6 patients had embryonal carcinoma and yolk sac tumor, 9 patients had embryonal carcinoma, yolk sac tumor and teratoma, 5 patients had teratoma and embryonal carcinoma, 4 patients had teratoma and yolk sac tumor and 1 patient had choriocarcinoma, yolk sac tumor and teratoma. There was a statistically significant difference between preoperative and postoperative mean NLR of the localized patients (preoperative NLR: 2.78±1.84, postoperative NLR: 1.57±0.58, p=0.001) but there was no statistically significant difference between preoperative and postoperative mean NLR of non-localized patients (preoperative NLR: 3.83±1.65, postoperative NLR: 3.52±2.79, p=0.576) (Table 2). Mean preoperative and postoperative NLR was significantly higher in non-localized patients compared to localized patients (Table-3). Thirteen seminomatous and 13 non-seminomatous, a total of 26 patients with localized TGCT had preoperative increased serum tumor markers (elevated HCG and/or AFP and/or LDH) which normalized after orchiectomy. Mean NLR of these patients signi-

Table 1 - Demographic characteristics of the patients.

Age, years, mean±SD (range)	37.83±9.98	(20-65)
Tumor size, cm, mean±SD (range)	4.45±1.93	(0.4-12)
Total number of patients, n (%)	61	(100)
Localized	45	(73.8)
Non-localized	16	(26.2)
Seminoma	36	(59)
Non-seminoma	25	(41)

Table 2 - Preoperative and postoperative neutrophil to lymphocyte ratio in localized and non-localized TGCT.

	Preop. NLR	Postop. NLR	P
Localized TGCT (mean±SD)	2.78±1.84	1.57±0.58	0.001
Non-localized TGCT (mean±SD)	3.83±1.65	3.52±2.79	0.576

TGCT = Testicular germ cell tumor; **Preop =** Preoperative; **Postop =** Postoperative **NLR =** Neutrophil to lymphocyte ratio

Table 3 - Comparison of neutrophil to lymphocyte ratio between localized and non-localized TGCT.

	Localized	Non-localized	P
Preop. NLR (mean±SD)	2.78±1.84	3.83±1.65	0.016
Postop. NLR (mean±SD)	1.57±0.58	3.52±2.79	0.004

TGCT = Testicular germ cell tumor; **Preop =** Preoperative; **Postop =** Postoperative; **NLR =** Neutrophil to lymphocyte ratio.

ficantly decreased from 3.10±2.13 to 1.62±0.59 postoperatively (p=0.010). Nineteen patients had normal preoperative serum tumor markers and all of these patients had localized seminomatous TGCT. Preoperative mean NLR of these patients was 2.43±1.28 and this ratio decreased to 1.55±0.57 postoperatively. This difference was also statistically significant (p=0.010) (Table-4).

Preoperative NLR of localized and non-localized TGCT were used to define an optimal cut-off value for the presence of non-localized TGCT. The optimal cut off value for non-localized TGCT was 2.56 with sensitivity 75% and specificity 60%, area under the receiver operating characteristics curve was 0.703 (95% confidence interval=47.6-92.2) (Figure-2).

Table 4 - Neutrophil to lymphocyte ratio of patients with preoperative elevated tumor markers that normalized postoperatively and patients with normal tumor markers.

	Preop. NLR	Postop. NLR	P
Preop. elevated markers (mean±SD)	3.10±2.13	1.62±0.59	0.010
Marker normal patients (mean±SD)	2.43±1.28	1.55±0.57	0.010

Preop = Preoperative; **Postop =** Postoperative; **NLR =** Neutrophil to lymphocyte ratio

Pearson's correlation coefficient was calculated as 0.302 indicating a positive correlation between tumor size and preoperative NLR that was statistically significant (p=0.018). Preoperative and postoperative NLR of localized TGCT were used to define an optimal cut off value for the presence of localized TGCT. The optimal cut off value for localized TGCT was 2.11 with sensitivity 84.44% and specificity 57.78%, area under the receiver operating characteristics curve was 0.73 (95% confidence interval=70.5-93.5) (Figure-1).

DISCUSSION

Although testicular cancer is the most common cancer in men under 40 years of age, it is curable in most of the cases (17). Germ cell tumors constitute 90% of all testicular cancers and serum tumor markers play a crucial rule in diagnosis, treatment and follow-up of patients with TGCT (3). NLR is an inexpensive and easily acquired inflammatory marker. Association of NLR and cancer was widely studied in various malignancies

Figure 1 - Receiver operating curve used to define optimal cut off value of NLR for localized TGCT.

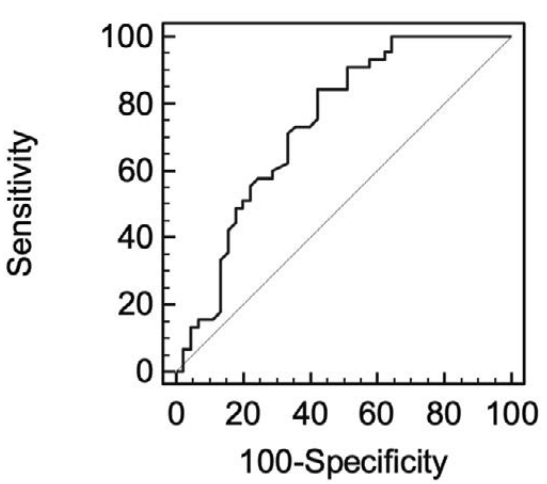
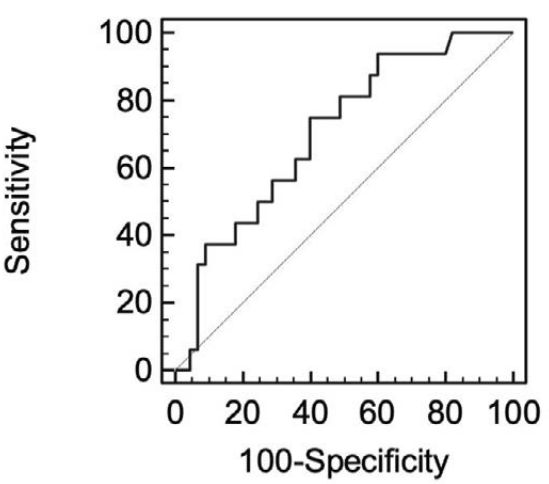


Figure 2 - Receiver operating curve used to define optimal cut off value of NLR for non-localized TGCT.



(14, 15) but the number of studies investigating the relationship between NLR and testicular cancer is quite low. Yuksel et al. compared preoperative NLR of patients with localized TGCT with varicocele patients who were included in the study as control group and found that NLR was significantly higher in patients with testicular cancer (18). In our study, we included both localized and non-localized patients and compared preoperative NLR with postoperative NLR. In localized patients there was a significant decrease in NLR after orchiectomy. Whereas, in non-localized patients there was not any statistically significant change in NLR value after surgery. It is known that patients with localized TGCT are mostly cured after orchiectomy whereas in non-localized patients there is still residual tumor. Maintaining an elevated NLR after orchiectomy is related with non-localized testicular cancer and observing a significant decrease in postoperative NLR suggests that patient has a localized disease. There is no other study in literature evaluating preoperative and postoperative NLR in testicular cancer. Park et al. investigated pretreatment and post-treatment NLR in patients with metastatic renal cell carcinoma receiving sunitinib (19). Post-treatment NLR was measured after first cycle of sunitinib treatment and they found that better tumor response was significantly associated with lower post-treatment NLR and larger reduction in NLR after first cycle. Morizawa et al. evaluated pretreatment and post-treatment NLR in patients with muscle invasive bladder cancer who underwent radical cystectomy (20).They stated that preoperative NLR decreased postoperatively and remained low in non-recurrent cases during follow-up. In recurrent cases although NLR decreased temporarily after radical cystectomy it increased significantly before recurrence was detected on imaging methods.

When mean preoperative NLR of localized patients was compared with non-localized patients, it was seen that NLR of non-localized TGCT patients was significantly higher. This significance was even higher when we compared mean postoperative NLR of these two groups as expected. This data suggest that as the disease progresses, there is an increase in NLR also. As far as we know there is not any other study in literature investigating the relationship of NLR with localized and non-localized TGCT. NLR has been showed to be an independent risk factor in various other urological tumors such as renal cancer, bladder cancer, upper tract urothelial carcinoma and prostate cancer (21). There is only one study regarding the predictive value of NLR on the prognosis of TGCT (13). Fifty-three patients with germ cell tumor were evaluated and no relationship was found between preoperative NLR and cancer specific survival or progression free survival.

AFP, HCG and LDH are important tumor markers that are helpful in diagnosis, staging and evaluation of response to the therapy (6). The persistence of elevated serum tumor markers after orchiectomy might indicate the presence of metastatic disease (macro-or microscopically), while the normalization of marker levels after orchiectomy does not rule out the presence of tumor metastases (4). In our study, twenty-six patients with localized TGCT had preoperative increased serum tumor markers (elevated HCG and/or AFP and/or LDH) that normalized postoperatively. Mean NLR of these 26 patients significantly decreased after orchiectomy. This finding shows us that there is a correlation between NLR and conventional serum tumor markers. Nineteen patients had normal serum markers preoperatively. All of these patients had localized seminomatous TGCT. When we compared preoperative NLR with postoperative NLR of this group we found that there is a significant decrease indicating that in seminomas with normal pre-orchiectomy serum markers, NLR can be used as an alternative marker.

Recently microRNAs, small noncoding RNAs involved in epigenetic regulation of gene expression, have been suggested as novel biomarkers for TGCT. Among these, microRNA-371a-3p has been proven to be the most promising. Dieckmann et al. found that microRNA-371a-3p has a sensitivity of 90%, specificity of 94% and positive predictive value of 97% for primary diagnosis of TGCT (22). It was also shown that its plasma levels began to decrease within hours after orchiectomy in patients with localized TGCT, remained elevated in patients with non-localized disease and also levels dropped after treatment were found to be elevated with relapse (22-24). These results

suggest that microRNA-371a-3p is a more useful marker for TGCT than both conventional markers and NLR. MicroRNA-371a-3p has not yet received regulatory approval but it is expected to be implemented in routine clinical practice soon (25).

We performed receiver operating characteristics curve analysis to define cut-off levels for NLR as a predictor of localized and non-localized TGCT. The optimal cut off value for localized TGCT was 2.11. The optimal cut off value for non--localized TGCT was 2.56. In their study, Yuksel et al. defined a cut off value of 2.06 for NLR in localized TGCT similar to our finding (18). Bolat et al. defined optimal cut off value of NLR for progression free survival as 3.55 and for cancer specific survival as 3.0 (13).

CONCLUSIONS

NLR appears to be a useful marker for predicting localized and non-localized TGCT in early postoperative period. A significant decrease in NLR after orchiectomy, especially a value of less than 2, indicates localized disease. Absence of a significant reduction after orchiectomy, especially a value greater than 2.5 indicates non-localized disease. In patients who have seminomas with normal conventional serum markers, NLR can be used as an alternative marker to differentiate localized disease. Our study has several limitations. We had a small group of patients and we did not evaluate relationship of NLR with recurrence and prognosis. According to our results NLR seems to be inferior to microRNA-371a-3p as a marker for TGCT. Also, we measured NLR one month after surgery. We didn't have any early postoperative measurement so we could not simultaneously compare NLR with conventional markers and we could not determine the half-life of NLR. Further large-scale and prospective studies are required to support our results. Also, it would be very valuable if it can be proven that NLR normalized after orchiectomy significantly increases with recurrence.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Znaor A, Lortet-Tieulent J, Jemal A, Bray F. International variations and trends in testicular cancer incidence and mortality. Eur Urol. 2014;65:1095-106.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59:225-49.
3. Leman ES, Gonzalgo ML. Prognostic features and markers for testicular cancer management. Indian J Urol. 2010;26:76-81.
4. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, et al. Guidelines on Testicular Cancer: 2015 Update. Eur Urol. 2015;68:1054-68.
5. Gori S, Porrozzi S, Roila F, Gatta G, De Giorgi U, Marangolo M. Germ cell tumours of the testis. Crit Rev Oncol Hematol. 2005;53:141-64.
6. Ehrlich Y, Beck SD, Foster RS, Bihrle R, Einhorn LH. Serum tumor markers in testicular cancer. Urol Oncol. 2013;31:17-23.
7. Stephenson AJ and Gilligan TD: Neoplasms of the Testis. In: AJ Wein et al., editor. Campbell-Walsh Urol. Elev. Ed., Philadelphia, Elsevier-Saunders. 2016, pp. 784-815.
8. Stevenson SM, Lowrance WT. Epidemiology and Diagnosis of Testis Cancer. Urol Clin North Am. 2015;42:269-75.
9. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436-44.
10. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. Mol Cancer Res. 2006;4:221-33.
11. Kusumanto YH, Dam WA, Hospers GA, Meijer C, Mulder NH. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis. 2003;6:283-7.
12. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883-99.
13. Bolat D, Aydoğdu Ö, Polat S, Yarımoğlu S, Bozkurt İH, Yonguç T, et al. Predictive value of preoperative neutrophil-to-lymphocyte ratio on the prognosis of germ cell testicular tumors. Turk J Urol. 2017;43:55-61.
14. Viers BR, Boorjian SA, Frank I, Tarrell RF, Thapa P, Karnes RJ, et al. Pretreatment neutrophil-to-lymphocyte ratio is associated with advanced pathologic tumor stage and increased cancer-specific mortality among patients with urothelial carcinoma of the bladder undergoing radical cystectomy. Eur Urol. 2014;66:1157-64.
15. Nora I, Shridhar R, Huston J, Meredith K. The accuracy of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as a marker for gastrointestinal malignancies. J Gastrointest Oncol. 2018;9:972-8.

16. Grimes N, Hannan C, Tyson M, Thwaini A. The role of neutrophil-lymphocyte ratio as a prognostic indicator in patients undergoing nephrectomy for renal cell carcinoma. Can Urol Assoc J. 2018;12:E345-8.
17. Chung P, Warde P. Testicular cancer: germ cell tumours. BMJ Clin Evid. 2016;2016.
18. Yuksel OH, Verit A, Sahin A, Urkmez A, Uruc F. White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: a simple secondary serum tumor marker. Int Braz J Urol. 2016;42:53-9.
19. Park YH, Ku JH, Kwak C, Kim HH. Post-treatment neutrophil-to-lymphocyte ratio in predicting prognosis in patients with metastatic clear cell renal cell carcinoma receiving sunitinib as first line therapy. Springerplus. 2014;3:243.
20. Morizawa Y, Miyake M, Shimada K, Hori S, Tatsumi Y, Nakai Y, et al. Neutrophil-to-lymphocyte ratio as a detection marker of tumor recurrence in patients with muscle-invasive bladder cancer after radical cystectomy. Urol Oncol. 2016;34:257.e11-7.
21. Luo Y, She DL, Xiong H, Fu SJ, Yang L. Pretreatment Neutrophil to Lymphocyte Ratio as a Prognostic Predictor of Urologic Tumors: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2015;94:e1670.
22. Dieckmann KP, Radtke A, Geczi L, Matthies C, Anheuser P, Eckardt U, et al. Serum Levels of MicroRNA-371a-3p (M371 Test) as a New Biomarker of Testicular Germ Cell Tumors: Results of a Prospective Multicentric Study. J Clin Oncol. 2019;37):1412-23.
23. Radtke A, Hennig F, Ikogho R, Hammel J, Anheuser P, Wülfing C, et al. The Novel Biomarker of Germ Cell Tumours, MicroRNA-371a-3p, Has a Very Rapid Decay in Patients with Clinical Stage 1. Urol Int. 2018;100:470-5.
24. van Agthoven T, Eijkenboom WMH, Looijenga LHJ. microRNA-371a-3p as informative biomarker for the follow-up of testicular germ cell cancer patients. Cell Oncol (Dordr). 2017;40:379-88.
25. Singla N, Lafin JT, Bagrodia A. MicroRNAs: Turning the Tide in Testicular Cancer. Eur Urol. 2019.

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SURGICAL TECHNIQUE

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Concurrent urinary and bowel diversion: Surgical modification with sigmoid colon that avoids a bowel anastomosis

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ABSTRACT

Objective: Cystectomy with urinary diversion is the gold standard for muscle invasive bladder cancer. It also may be performed as part of pelvic exenteration for non-urologic malignancy, neurogenic bladder dysfunction, and chronic conditions that result in a non-functional bladder (e.g., interstitial cystitis, radiation cystitis). Our objective is to describe the surgical technique of urinary diversion using large intestine as a conduit whilst creating an end colostomy, thereby avoiding a primary bowel anastomosis and to show its applicability with respect to urologic conditions.
Materials and Methods: We retrospectively reviewed five cases from a single institution that utilized the described method of urinary diversion with large intestine. We describe operative times, hospital length of stay (LOS), and describe post-operative complications.
Results: Five patients with a variety of urologic and oncologic pathology underwent the described procedures. Their operative times ranged from 5 hours to 11 hours and one patient experienced a Clavien III complication.
Conclusion: We describe five patients who underwent this procedure for various medical indications, and describe their outcomes, and believe dual diversion of urinary and gastrointestinal systems with colon as a urinary conduit to be an excellent surgical option for the appropriate surgical candidate.

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INTRODUCTION

Cystectomy with urinary diversion is the gold standard for muscle invasive bladder cancer. It also may be performed as part of pelvic exenteration for non-urologic malignancy, neurogenic bladder dysfunction, and chronic conditions that result in a non-functional bladder (e.g., interstitial cystitis, radiation cystitis). The hallmark of all forms of urinary diversion is the use of bowel to substitute for the excised bladder. Potential gastrointestinal segments include stomach, jejunum, ileum, and colon. The choice of segment is based on multiple patient factors, including the type of diversion, prior abdominal and bowel surgery, and potential risk of metabolic abnormalities post-operatively. Ileal conduit is the most common form of urinary diversion, first described by Seiffert in 1935 and then popularized by Bricker. As stated by Hautmann (1), the most important factors when considering conduits are adequate cancer control, lower complication rates and feasibility

to continue activities of daily living comfortably.

Urinary diversions have evolved significantly over time. Early diversions of the late 1800's and early 1900's typically anastomosed a portion of the urinary tract to a segment of bowel that remained in continuity with the remainder of the GI tract. Examples include ureteroproctostomy for bladder extrophy, direct anastomosis of the trigone with bowel using two layers (Maydl) and anastomosis of the ureters to cecum (2).

Historically, rectal and rectosigmoid bladder conduits were introduced in the 1890's but with minimal success until the 1950s when Boyce and Vest described and performed a two-stage technique for a rectal bladder in exstrophy patients (3). Gastric and transverse colon conduits became popular in the 1960s when radiotherapy was used commonly for pelvic malignancies, as these were less affected by radiation field.

In 1940, Bricker used the isolated sigmoid colon as a conduit in four patients and placed the urostomy stoma near the colostomy (4). This technique was then revised by Turner-Warwick in the 1950s when he placed the sigmoid colostomy on the left abdomen and the urinary conduit with sigmoid colon in the right abdomen, as we will describe below (5). As time passed, others explored continent diversions using ileum and ileocecal neobladders. The late 20th century ushered in the modern-day era of continent urinary diversion, both continent cutaneous and orthotopic neobladder.

Through history, the ileal segment has become the most utilized for multiple reasons including ease of mobilization and less risk of intestinal malabsorption, electrolyte abnormalities and chronic diarrhea. Despite this, there are several literature reviews highlighting the negative early postoperative and long-term effects of primary bowel anastomosis which is typically performed after isolating a bowel segment for urinary diversion, including postoperative ileus, increased hospital length of stay, fistula formation, anastomotic breakdown, bowel obstruction, intestinal stenosis (6).

In cases in which the patient has a primary bowel condition in addition to one of the urinary indications for diversion, it may be beneficial to consider using sigmoid colon as previously described, to create two concurrent diversions-urostomy and colostomy. Patients requiring urinary diversion may have concomitant bowel conditions that favor diversion such as malignancy, neurogenic bowel with severe constipation, non-healing wounds, fistulas and chronic diarrhea. Considering these indications, there are several patient conditions that may benefit from simultaneous urinary and bowel diversion such as neurologic diseases (e.g., spinal cord injury, multiple sclerosis), which result in neurogenic bladder and bowel, and locally advanced pelvic malignancy involving and/or invading the genitourinary and gastrointestinal tract. Barboglio Romo et al. reviewed 46 cases of patients with double diversions, comparing those who underwent urinary diversion after colostomy versus simultaneous creation, and found no independently associated risk of adverse events with concurrent creation (7).

Here we describe the surgical technique for an infrequently utilized technique for simultaneous urinary and bowel diversion with a colonic conduit to avoid a bowel anastomosis and minimize the amount of bowel taken out of continuity. Theoretical benefits include decreased complications and faster recovery. We describe our operative technique in detail, review five cases performed at our institution, and discuss the potential advantages of this surgical procedure.

Surgical Technique

The patient is given a mechanical bowel preparation with either magnesium citrate or polyethylene glycol. An orogastric tube is placed by anesthesia. A urethral catheter is placed to gravity drainage after sterile preparation and draping. The table is slightly flexed. A lower midline incision is utilized from the umbilicus to the pubic symphysis. The peritoneum is carefully entered and a Bookwalter retractor is placed. Adhesions are lysed as necessary. The ureters dissected free in the retroperitoneum and divided distally at the ureterovesical junction. A complete or supra-trigonal cystectomy is performed depending on the indication for surgery. At this point, our general or colorectal surgery colleagues join the operation.

In review of the surgical anatomy and blood supply of the large intestine, we pay close attention to the branches of the inferior mesenteric artery, the left colic artery to the descending colon and the superior hemorrhoidal artery to the sigmoid colon and rectum (Figure-1). The expertise of a general or colorectal surgeon to delineate the mesenteric blood supply and help decide where to make the mesenteric windows cannot be understated. The descending colon is mobilized from its retroperitoneal attachments, and a division site between the descending colon and sigmoid colon is chosen. The rectosigmoid junction is identified. The GIA stapling device is utilized to divide the colon at the junction of the descending and sigmoid colon and also at the rectosigmoid junction. The rectosigmoid mesentery is divided using an energy device or ties radially from the bowel, dividing the arc of the superior hemorrhoidal artery as it passes the rectosigmoid junction. The mesentery at the junction of the descending and sigmoid colons are divided as well up to the bifurcation of the inferior mesenteric artery, taking care to preserve the both branches of the bifurcation of the inferior mesenteric artery (Figure-2). If mesenteric length limits reach of the descending colon to the abdominal wall, the left colic artery can be divided at the bifurcation of the inferior mesenteric artery, such that the descending colon will draw its blood supply from the middle colic artery via the marginal artery. The rectal stump is left in place as a Hartman's Pouch for patients with benign disease, and the sigmoid is now free for mobilization to the level of the skin (Figure-3). The rectum is resected prior to beginning the diversion for those with malignancy. The descending colon with the GIA staple line will later be used to fashion the colostomy. The ends of both ureters are spatulated for 1-2cm. Ureteroenteric anastomosis is performed in non-refluxing, running fashion with either 4-0 Vicryl or 4-0 PDS (Figure-4). The ureters are anastomosed to the taenia of the sigmoid conduit in a proximal location. Urinary diversion stents are utilized. Because the sigmoid colon is utilized, the left ureter does not require tunneling under the sigmoid mesentery as would be done for an

Figure 1 - Large bowel with blood supply.

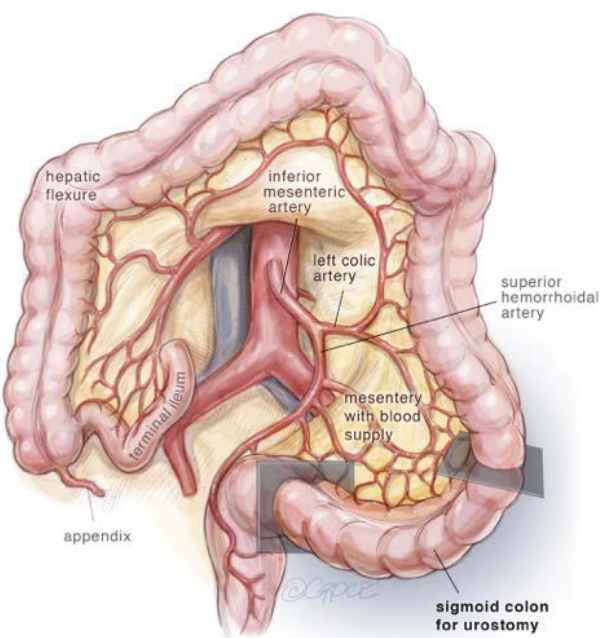


Figure 2 - Sigmoid isolation for urinary conduit.

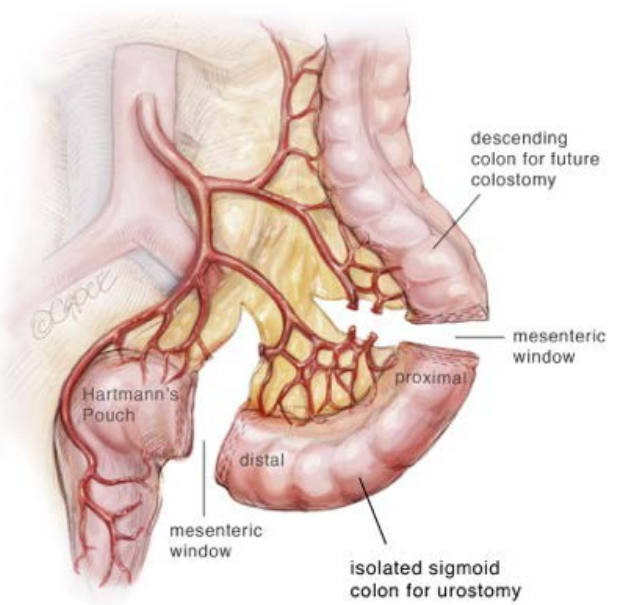


Figure 3 - Mobilization of sigmoid conduit for urinary diversion.

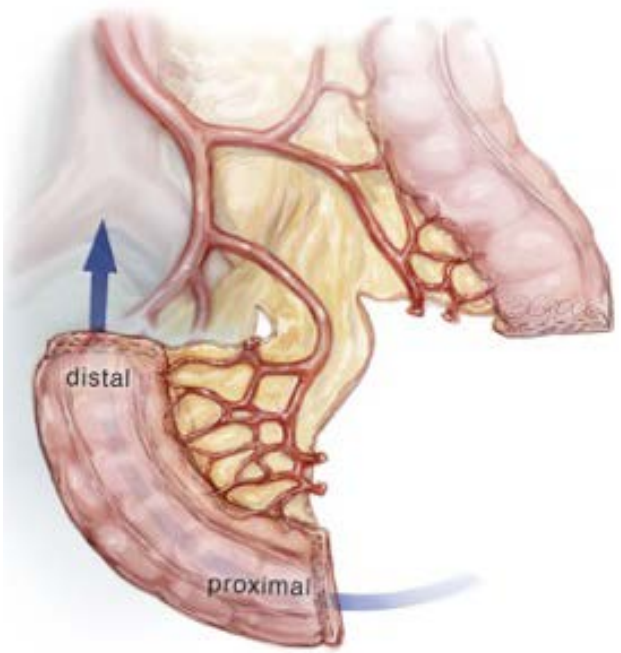
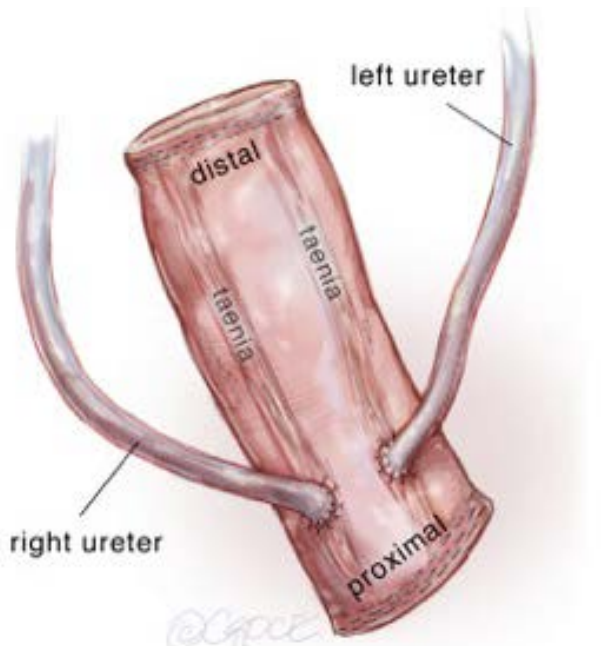
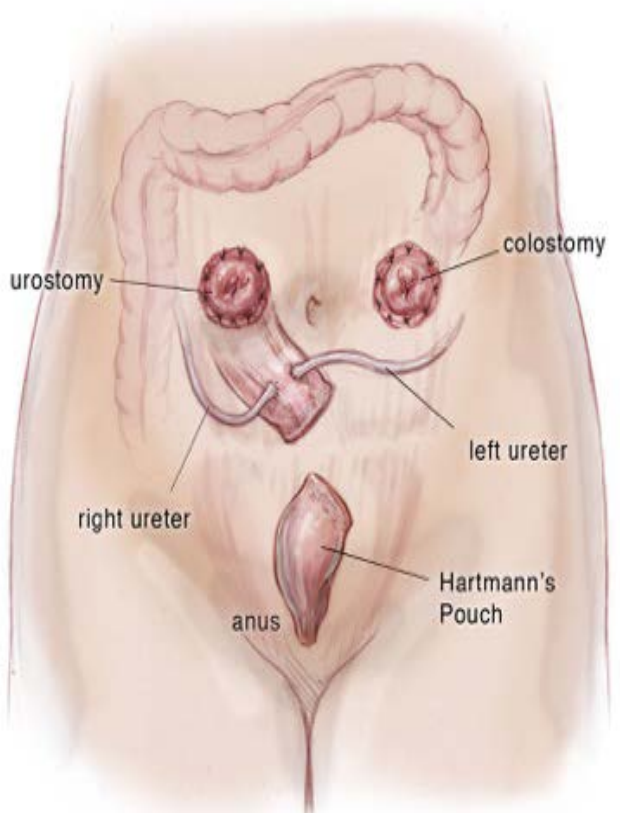


Figure 4 - Uretero-sigmoid anastomosis.



ileal conduit. The distal end of the sigmoid conduit is then brought out through the skin, preferably in the right lower quadrant, and the stoma is created in a standard Brooke fashion (6). If there is difficulty reaching the right lower quadrant due to body habitus, tight mesentery, or other anatomic restriction (e.g., baclofen pump on the right side of the abdomen in one of our cases), the urostomy can be seated in the left lower quadrant with the plan for the colostomy to be placed superiorly. The descending colon is then utilized for the colostomy in the left lower quadrant (Figure-5). The abdominal fascia is closed before opening the staple line and seating the colostomy.

Figure 5 - Final urinary and bowel diversion orientation.



Case 1

SD is a 64 year-old gentleman with locally advanced rectal cancer who underwent neoadjuvant radiation therapy and was then lost to follow-up for planned surgical resection. He subsequently developed urinary retention with bilateral hydronephrosis in the setting of locally advanced disease without distant metastasis with prostatic and bladder base involvement of rectal cancer. After completing 10 cycles of FOLFOX

chemotherapy, he consented to pelvic exenteration (cystoprostatectomy and abdominal-perineal rectal resection) with colostomy and concurrent sigmoid conduit urinary diversion. On September 2014, he underwent the above surgery with our described technique for urinary and bowel diversion. His postoperative course was complicated by acute blood loss anemia requiring blood transfusion and prolonged ileus, for which he received TPN and eventually tolerated a regular diet. He was discharged on POD#14.

Case 2

DB is a 32 year-old T4 paraplegic male secondary to gunshot wound in 2008 with chronic decubitus ulcers, colitis and osteomyelitis of the hips. He had previously undergone multiple open wound debridements and myocutaneous flap coverage. He had neurogenic bladder managed with indwelling urethral catheter. He underwent urodynamics testing that showed a bladder capacity of only 44cc. Given his extensive decubitus ulcers, neurogenic bladder with small capacity, and ventral penile shaft erosion secondary to indwelling catheter, decision was made for cystectomy with urinary and intestinal diversion. He underwent the above surgery in January 2015 utilizing our described technique. We placed both the urostomy (inferior) and colostomy (superior) on the left side of the abdomen because of a subcutaneous baclofen pump located on the right side and a gastrostomy tube in the mid-upper abdomen. His postoperative course was remarkable for an ileus on POD#6 that resolved quickly when G tube was placed to gravity. He was advanced again to clear liquid diet on POD#8 and regular diet on POD#9. He was discharged on POD#9.

Case 3

RR is a 52 year-old C5-C7 quadriplegic male with recurrent nephrolithiasis and neurogenic bladder and bowel. He experienced difficulty emptying his bladder despite a distant history of sphincterotomy and refused intermittent catheterization. During one of his ureteroscopic stone surgeries, he was found to have a flat bladder lesion on the floor of bladder that was biopsied and found to be invasive, moderately differentiated, squamous cell carcinoma. He was concurrently followed by colorectal surgery for hemorrhoids, rectal prolapse and atonic anal sphincter with chronic constipation from neurogenic bowel. Given his bladder disease, decision was made to address his colorectal conditions surgically to optimize his quality of life. In July 2015 he underwent radical cystoprostatectomy and urinary and bowel diversion with our described technique. Intraoperatively, his mesenteric vessels were notably robust. The proximal division was made just distal to the takeoff of the left colic artery from the inferior mesenteric artery. The sigmoid colon was then measured 20 centimeters and the peritoneum overlying the distal sigmoid was incised to increase length. The IMA and superior hemorrhoidal arteries were intact. Urostomy was seated on the right and colostomy on the left. His postoperative course was unremarkable. He was discharged to rehabilitation on POD#4 with no early or late complications.

Case 4

DS is a 37 year-old non-smoking gentleman with cerebral palsy with multifocal, recurrent, high grade, non-muscle invasive urothelial carcinoma of the bladder which ultimately progressed to muscle invasive disease. At baseline, he voided independently but did exhibit signs of neurogenic bladder. His other comorbidities included sacral-decubitus ulcers and diarrhea-predominant irritable bowel syndrome (IBS) with fecal incontinence resulting in significant weight loss requiring gastrostomy tube placement. In August 2015, he underwent radical cystoprostatectomy with urinary and bowel diversion utilizing our described technique. Intraoperatively, there was notable difficulty with positioning due to flexion contractures. The sigmoid colon was able to be isolated for 15cm for a conduit. The colon was fortunately extremely redundant. The inferior mesenteric artery did need to be ligated for mobilization of the colonic segment. The mesentery was divided such that the superior hemorrhoidal artery supplied the sigmoid urinary conduit, and the left colic artery supplied the end colostomy. Post-operatively, he was slowly advanced to a regular diet on POD#5. His post-operative cour-

se was unremarkable and he was discharged on POD#8 with no early or late complications.

Case 5

SA is a 63 year-old gentleman with locally advanced rectal carcinoma who underwent exploratory laparotomy and end sigmoid colostomy for large bowel obstruction. The primary tumor was seen on MRI to be locally invasive into the posterior prostate, seminal vesicles and perirectal lymph nodes. After completing chemoradiation, he was taken to the operating room for pelvic exenteration and urinary diversion. The plan was to leave the existing colostomy on the patient's left abdomen, and create an ileal conduit in the right hemi-abdomen, however, during the case the ileum appeared to have radiation related changes and the bowel appeared edematous and firm. Given that no significant segment of bowel appeared safe for removal and there was concern about well-healing bowel anastomosis, decision was made to use the existing colostomy as a urostomy. The colostomy was washed out thoroughly and the ureters were implanted near the taenia coli after the colon was divided 20cm from the ostomy. The remaining large bowel was then mobilized towards the right hemicolon and matured as a new transverse loop colostomy. The patient had an uneventful recovery with diet advanced to clears on POD#2, solids on POD#8 after return of bowel function. He was discharged on POD#10 with no complications.

Table-1 summarizes the five patients described above noting diagnosis, operative times, estimated blood loss (EBL), length of stay

Table 1 - Case details for five cases with urinary diversions using colonic conduits.

Patient	Diagnosis	Operative times	EBL	LOS (days)	Early Complications [7] (30 days)	Late Complication [7] (90 days)
SD	Advanced rectal cancer involving prostate and bladder	10h 25m	1500 mL	14	Clavien II – acute blood loss with transfusion, TPN requirement for ileus	Clavien IIIB – Small bowel obstruction secondary to parastomal hernia requiring exploratory laparotomy
DB	T4 paraplegic with colitis, neurogenic bladder and decubitus ulcers	5h 39m	200 mL	9	Clavien IIIB – necrotizing right thigh fasciitis requiring debridement	None
RR	C5-7 quadriplegic with neurogenic bowel, rectal prolapse/ chronic constipation and invasive bladder squamous cell carcinoma	7h 0m	700 mL	4	None	None
DS	Cerebral palsy with high grade muscle-invasive urothelial carcinoma with irritable bowel syndrome	6h 6m	500 mL	8	None	None
SA	Locally invasive rectal adenocarcinoma into prostate and seminal vesicles	7h 1m	50 mL	10	None	None

(LOS) and early (30 day) and late (90 day) complications by Clavien-Dindo classification.

DISCUSSION

Though other groups have compared outcomes of simultaneous urinary and bowel diversion to staged surgery (7), the surgical technique has not been clearly described prior to this article. The surgical description with support from the five cases demonstrate the types of patients who may benefit from this operation.. The cases highlight minor modifications that can be pragmatic (e.g., placing both urostomy and colostomy on the same side of the abdomen is easily achieved, or using an existing conduit for urinary diversion, and re-siting the colon).

This short series emphasizes a team approach between urologic and general (or colorectal) surgeons. Too often in today's healthcare system is patient care fragmented among various specialists, and this can be most burdensome for patients that would benefit from multiple surgical procedures. For patients who would benefit from double diversion, efforts should be made to do concurrent surgery when possible for this higher-risk surgical population. Patient comorbid factors and malnutrition are strong incentives to minimize the number of surgical procedures. In addition, subsequent surgical procedures yield the added risk and complexity of adhesions and scarring.

For this surgical technique, the average OR times are variable but not outside the range for a standard cystectomy and urinary diversion. Interestingly, the four institutions involved in Romo's study found an increase in adverse events related to increase in operative time (7) for either simultaneous double diversion or staged diversions. In this small cohort, complications seemed similar to those seen after urinary diversion alone, but certainly more cases need to be completed to make any definitive conclusions. The major theoretical benefit is forgoing the bowel anastomosis. This simplifies the operation, may speed up recovery of bowel function, and virtually eliminates the risk of bowel leak in this malnourished group with a strong preponderance for slow fecal transit and constipation. By virtue of using the sigmoid colon, the left ureter is not tunneled under the mesentery to the right side. This can be very advantageous for obese patients where the traditionally tunneled left ureter is often placed on undesirable tension for the anastomosis. We observed no early or late ureteral strictures in our small series of 5 cases. In this patient population, adequate space to place two stomas is often at a premium. Body habitus, contractures, prior surgery, percutaneous drains (e.g., G-tube), and subcutaneous implants (e.g. baclofen pump) can limit the surface area required for both urostomy and colostomy. By utilizing the same mesentery for both diversions, placing both stomas on the same side of the abdomen is feasible, as described in one of our cases. This technique does largely rely on a mobile sigmoid colon and mesentery. The distal end of the sigmoid must be able to rotate significantly cephalad to reach the skin without tension. Other limitations, such as pelvic radiation affecting the sigmoid colon and its blood supply, can be potential factors that would preclude this operative technique. For advanced bladder cancer, radiation is less often utilized, but for gynecologic and colorectal malignancies this issue could arise more frequently.

In summary, we describe our surgical technique for concurrent urinary and bowel diversion utilizing the descending and sigmoid colon. The key steps of this operation are emphasized, in particular the management and appropriation of the blood supply to both the colostomy and urostomy. This technique avoids a bowel anastomosis, minimizes the amount of bowel taken out of continuity, allows for less tension on the left ureter, and provides more flexibility for where to place the urostomy. The authors believe this surgical technique is an excellent option for patients requiring both intestinal and urinary diversions.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Hautmann RE. Urinary diversion: ileal conduit to neobladder. J Urol. 2003;169:834-42.
2. Webster GD. Peterson AC. History of urinary diversion techniques. Urinary Diversion. Taylor and Francis, New York, 2005. 1-20.
3. Saber A. Urinary diversion: Historical aspect and patient's satisfaction. Urol. Nephrol. Open Access J 1.2014: 14-21.
4. Bricker EM. Bladder substitution after pelvic evisceration. Surg Clin North Am. 1950;30:1511-21.
5. Warwick RT. Technique for the separate diversion of urine and faeces. Lancet. 1959;1:1021-2.
6. Wein, Alan J., et al. "Use of intestinal segments in urinary diversion." Campbell-Walsh urology 10th Edition (2012): 3:2411-449.
7. Barboglio Romo PG, Santiago-Lastra Y, Myers JB, Pathak P, Elliott SP, Cotter KJ, et al. Multi-institutional Outcomes for Simultaneous and Staged Urinary and Fecal Diversions in Patients Without Cancer. Urology. 2018;118:202-7.
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.

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EXPERT OPINION

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Are specialized sperm function tests clinically useful in planning assisted reproductive technology?

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CASE STUDY

40-year-old male patient and 32-year-old female partner, with a history of primary infertility of two years duration. The workup revealed idiopathic mild oligoasthenoteratozoospermia, and no apparent female infertility factors. The couple has failed three intrauterine insemination (IUI) cycles, planning more IUI cycles but also considering in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI).

Keywords:

Infertility, Male; Therapeutics; Reproductive Techniques, Assisted

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INTRODUCTION

The use of sperm function tests in the above scenario is only valid if test results help us to guide clinical management and provide benefit to patients at acceptable costs. Reviewing the published literature over the last five years, specifically concerning the clinical utility of specialized sperm function tests (SSFTs) for male infertility diagnosis, intrauterine insemination (IUI), and assisted reproductive technology (ART) outcomes, it becomes evident that the current research shifted to tests that assess sperm function at the molecular level. Nevertheless, a few studies still explore the use of sperm fertilizing ability, such as sperm capacitation and acrosome reaction (AR), as potential biomarkers of sperm function.

Tests evaluating sperm fertilizing ability

In a 2018 prospective study, Schinfeld and colleagues (1) evaluated pregnancy rates according to the results of a commercially available assay that measures the sperm fertilizing ability by assessing capacitation in 91 couples undergoing IUI. The authors found that the likelihood of achieving pregnancy by IUI was about 3-fold higher when sperm with the so-called 'high fertilizing potential' was

used for insemination. According to this study, the sperm capacitation test could help the clinician to decide whether a couple should insist on IUI or better move to ART.

In another 2018 study, Xu and colleagues (2) examined the utility of the AR test to predict fertilization in 485 couples undergoing conventional in vitro fertilization (IVF). The authors found that the percentage of sperm exhibiting spontaneous AR in neat semen predicted fertilization rates (FR). An area under the curve (AUC) of 0.85 ($p=0.005$) for low (FR<30%) or total fertilization failure was achieved using a threshold of 9.5%. Thus, according to their results, the AR test could help the doctor to decide whether a couple is eligible for conventional IVF or better move to intracytoplasmic sperm injection (ICSI).

Tests measuring oxidative stress

Oxidative stress (OS) tests have also been explored concerning male infertility diagnosis and ART outcomes. In a 2017 study by Agarwal and colleagues, the authors measured the oxidation-reduction potential (ORP) in 594 infertile men and 101 fertile controls using a commercially available assay, which provides a snapshot of the balance between oxidants and reductants in the semen. They found that that ORP levels were twice higher among infertile men (vs. controls; $p<0.001$), and that the ORP cutoff of 1.42 $mV/10^6$ sperm distinguished fertile from infertile men with 60.6% sensitivity, 74.3% specificity, and 93.3% positive predictive value (3).

Using the same assay, a study from South Africa involving 51 couples showed that ORP results might be useful to predict low fertilization (defined as FR<66.7%) as well as live birth rates (LBR) by ICSI, with AUCs of 0.81 ($p=0.002$) and 0.77 ($p=0.0007$), respectively (4). The authors also showed that ORP results were correlated with sperm DNA fragmentation (SDF) values obtained with the use of the TUNEL assay ($r=0.53$; $p=0.0001$), which is not surprising given the well-known association between OS and SDF.

Tests evaluating sperm DNA damage

Most current data on the clinical utility of SSFTs concern SDF tests. In fact, results of a 2017 survey study showed that SDF tests are commonly requested by fertility specialists, with TUNEL, sperm chromatin structure assay (SCSA), sperm chromatin dispersion (SCD) test, and Comet assay being the four most common assays utilized to measure SDF (5). The average reported cost for a SDF test was 170 US dollars (±123). Among the top 3 indications for test requests, i.e., (i) pregnancy failure after IUI, IVF, or ICSI, (ii) recurrent miscarriage after IUI, IVF, or ICSI, and (iii) recurrent natural pregnancy loss (RPL), the case of couples with failed IUI or ART ranked first. Interestingly, about two out of three responders said that abnormal SDF levels would affect their clinical management.

These results are actually not surprising given the well-established association between sperm DNA damage and risk of infertility (6-11). It has also been suggested that SDF negatively affects IUI and ART outcomes (12-15). Moreover, the sperm genetic defect could be transferred via ART, thus potentially affecting the health of resulting offspring (16, 17).

Indeed, big data from a compilation of 28 studies including 1294 fertile men and 2883 infertile men indicate that SDF testing can be a potent tool for male infertility diagnosis, with thresholds of 20% having high accuracy (AUC: 0.844; $p<0.01$) to distinguish fertile from subfertile men (18). These results are consistent with those of a landmark study by Ribas-Maynou et al., which showed that there exist high correlations ($r>0.70$; $p<0.001$) and similar thresholds among SCSA (18.9%), SCD (22.7%), and TUNEL (20.0%) values concerning male infertility diagnosis. In the above study, the alkaline Comet assay was also accurate (AUC: 0.93) for male infertility diagnosis, but with higher SDF thresholds (45.4%) than the three other tests (19).

In our Clinic, SDF results in a consecutive cohort of 1639 men - using the SCD test - indicate that over 50% of the patients have values of 20% and higher. And 25% of our population have SDF values of 30% or higher (20). In general, our group follows the practice recommendations issued by the Society for Translational Medicine in 2017 to request the SDF test (21). According to these evidence-based guidelines, the main clinical scenarios for testing include (i) Clinical varicocele (in particular, grades 2 and 3 varicocele with normal conventio-

nal semen parameters, and grade 1 varicocele with borderline/abnormal conventional semen parameters), (ii) Unexplained infertility/IUI failure/RPL, (iii) IVF and/or ICSI failure, and (iv) Borderline abnormal (or normal) semen parameters with risk factor (e.g., smoking, obesity, gonadotoxin exposure).

IUI failure seems to be an excellent indication to recommend the test as patients with high SDF would better benefit from ART than IUI. In a 2007 study involving 387 IUI cycles, LBR of 19% and 1.5%, respectively, were achieved when inseminations were carried out with semen of men with normal and abnormal SDF values, measured by the TUNEL assay (6). These results are consistent of those of a recent systematic review and meta-analysis of ten studies and 2839 cycles that showed a strong association between SDF and IUI outcomes (15). In this study, the relative risk of pregnancy failure by IUI was significantly higher in couples whose male partners had high SDF (RR 0.34; 95% CI 0.22-0.52; I^2=1.2%; P<0.001).

Thus, for our patients with IUI failure, like the case study under discussion, SDF testing could help guide clinical management, albeit the quality of the evidence supporting this recommendation is not very high (21). For such couples, ART, in particular, ICSI, would be a better alternative to overcome SDF-related infertility, possibly due to the technical differences between the two methods of fertilization (6, 22).

However, despite the better results with ART in cases of high SDF, sperm chromatin damage seems to adversely affect both conventional IVF and ICSI pregnancy outcomes. In a 2017 review aggregating the data from 70 studies and over 17,000 ART cycles, the likelihood of pregnancy failure was higher in couples whose male partners had high SDF (IVF studies: OR 1.15, 95% CI 1.05-1.27, p=0.003; ICSI studies: OR 1.12, 95% CI 1.01-1.25, p=0.025). The magnitude of the effect varied with the type of SDF assay (TUNEL: OR 1.85; 95% CI 1.52-2.26, p<0.0001; SCD: OR 1.16, 95% CI 1.02-1.32, p=0.023; Comet: OR 4.15, 95% CI 3.04-5.68, p<0.0001; SCSA: OR 1.14, 95% CI 1.04-1.25, p=0.004) (14). Notably, the authors showed that the clinical utility of the test concerning pregnancy prediction increased when female infertility factors were excluded (1704 cycles; OR 1.37, 95% CI 1.11-1.68, p=0.003), thus highlighting the importance of SDF to ART outcomes.

Added to the increase in the risk of pregnancy failure, SDF also increases the risk of miscarriage in pregnancies achieved with the use of both conventional IVF and ICSI (16 studies; RR: 2.2; 95% CI: 1.54-3.03; p<0.00001) (14, 23). Therefore, SDF test results might be used not only to prognosticate ART outcomes but also guide clinical management, as it has been suggested that ICSI with testicular sperm in preference over ejaculated sperm could be a valid option to overcome infertility in cases of high SDF (21).

A possible explanation for the better ICSI outcomes with testicular sperm relates to the ~3-fold lower SDF in testicular specimens than ejaculated counterparts (24). The susceptibility of sperm chromatin to oxidative attack, particularly during epididymis transit, is well-established and might explain the low testicular sperm positivity for SDF among infertile men (25).

The above findings seem to translate in better reproductive outcomes when testicular sperm rather than ejaculated sperm are used for ICSI in couples whose male partners have confirmed high SDF in the semen. In a systematic review of four ICSI studies including 507 cycles, the use of testicular sperm for ICSI improved clinical pregnancy rates (OR 2.42, 95% CI 1.57-3.73; I^2=34%, p<0.0001), decreased miscarriage rates (OR 0.28, 95% CI 0.11-0.68, I^2=11%, p=0.005, and increased LBRs (OR 2.58, 95% CI 1.54-4.35, I^2=0%, p=0.0003) (26). After that, confirmatory evidence concerning the effectiveness of testicular sperm for ICSI has been reported by several independent groups (reviewed by Lopes & Esteves (27)). Thus, despite the still limited evidence and lack of randomized controlled trials, the above data overwhelmingly suggest that the SDF test could guide management by selecting the couples who might benefit from ICSI with testicular sperm.

As far as the health of resulting offspring is concerned, no study has yet compared ICSI with testicular versus ejaculated sperm when both are available. However, the published data concerning the use of testicular sperm from azoospermic men are overall reassuring with regards to the most critical outcomes (28-30). Moreover, data from the

group of Cornell, using comprehensive chromosomal evaluation by next-generation sequencing (NGS) analysis, indicate that testicular sperm have not only lower DNA fragmentation but also lower aneuploidy rates than ejaculated sperm (testicular sperm: 1.2%; ejaculated sperm: 8.4%; p=0.02) (31). Lastly, recent data from our group corroborate the safe utilization of testicular sperm. In a 2019 study evaluating 363 couples undergoing ICSI, we looked at the likelihood of a blastocyst being euploid -by NGS- according to the type of sperm used for ICSI (32). We found no differences in the probability of a metaphase oocyte to turn into a euploid blastocyst when ICSI was carried out with the use of testicular or ejaculated sperm taken from men with high SDF, thus suggesting that testicular sperm is as healthy as, if not healthier than, ejaculated sperm.

DISCUSSION

Using SSFTs in clinical practice, the clinician can, first of all, make a more accurate diagnosis concerning the male factor contributing to infertility. This might help to identify and treat the underlying conditions with the aim of improving sperm function, possibly impacting positively on delivery rates of healthy offspring. Furthermore, better patient counseling can be provided concerning treatment outcomes, and lastly, results of tests could help us guide clinical management towards more personalized and effective ART.

Let us consider the following scenario. An IVF Center performs about 1,000 cycles a year with an overall clinical pregnancy rate (CPR) of about 40%. According to the best available evidence from 14 IVF and ICSI studies involving 2,756 couples, the risk of miscarriage is increased in couples with high SDF subjected to IVF or ICSI with ejaculated sperm (OR 2.7, 95% CI:1.4-5.1, p=0.003) (13). Translating the OR to plain numbers, it means that this hypothetical Clinic could lose about 82 pregnancies in a year as a result of SDF, thus leading to an absolute LBR reduction of about 20%. Naturally, fertility clinics cannot afford such a loss, and therefore, they should care about SDF testing.

Actually, none of us should ignore the factors affecting the health of sperm and the resulting offspring. Although ICSI is an extraordinary achievement, evidence accumulated over the last 25 years indicates that the health of ICSI offspring might be affected, in particular, when the subfertility is of male origin (30). The health issues potentially related to male subfertility and use of ICSI includes congenital malformations, childhood cancer, psychological and neurological development abnormalities, infertility, and cardiometabolic profile impairment (reviewed by Esteves et al. (30)).

We advocate the use of SSFTs, in particular SDF, to identify and treat the underlying conditions associated with abnormal sperm function (20, 33, 34). For instance, let us consider the case of varicocele, whose pathophysiology is linked to OS that is a well-known causative factor for SDF. Data from 21 studies and 1270 infertile men indicate that varicocele repair improves sperm chromatin integrity with an average absolute reduction in SDF values of about 8% (35). In this review, the reduction in SDF after varicocele repair was shown to be translated into a higher chance of achieving both natural and assisted pregnancies; the mechanism seems to be related to the alleviation of OS. Emerging evidence also indicates that other interventions, including lifestyle changes, treatment of genital tract infections, and FSH therapy could help to reduce SDF (20, 34).

Therefore, sperm DNA testing can be undoubtedly useful in planning ICSI. A high SDF test result calls for action, which includes the treatment of underlying conditions to improve both sperm chromatin integrity and fertility prospects potentially. When no treatable condition is identified, consideration to ICSI with testicular sperm should be given (Figure-1) (24, 36). However, given the risks associated with sperm retrieval (37-40), ICSI with testicular sperm should be reserved for men with confirmed sperm DNA damage or severe oligozoospermia/cryptozoospermia (41); this is one of the reasons why testing is important.

According to the data of a prospective study by our group comparing reproductive outcomes in 172 oligozoospermic men with high SDF treated by ICSI with ejaculated and testicular sperm, five couples have to be treated by ICSI with testicular sperm (versus ICSI with ejaculated sperm) to achieve one additional delivery in couples whose male partners have oligozoospermia

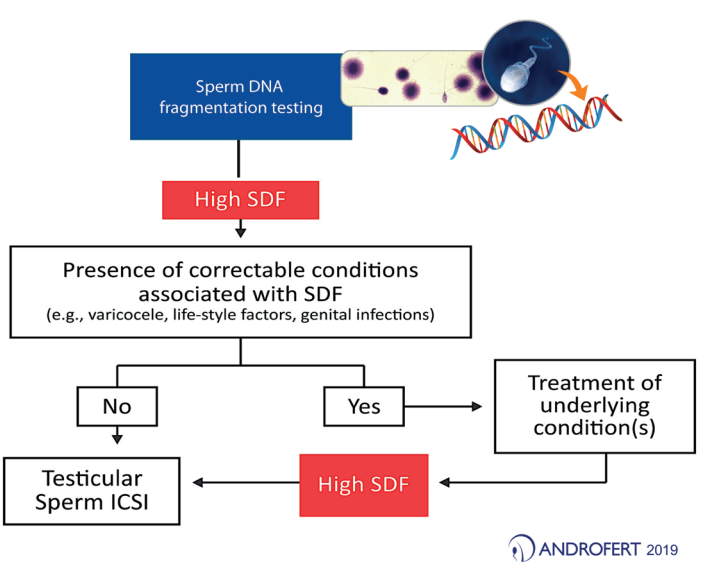
and high SDF in semen (42). Whereas this might represent more invasive treatments for men, it would translate in fewer treatments for women, who are generally the ones carrying the burden.

Lastly, it is easy to criticize the SSFTs based on the grounds of low predictive values and variable thresholds (43, 44). However, it is essential to understand that infertility is a couple's problem; it is, therefore, evident that a single test from just one side will be always limited to provide the full picture (45-50). More important is to acknowledge the fact that high SDF increases the risk of an adverse reproductive outcome, even with ICSI, and that the risk is modulated by female age. The equation relating the continuum of SDF values and maternal age makes much more sense than fighting about absolute thresholds and predictive values, in a scenario where pregnancy rates in the best circumstance will rarely go beyond 50%. Naturally, sperm DNA testing does not replace the adequate male infertility evaluation, but they can certainly add independent information that could help us to offer better care to our patients. So, let us think clinical (and less critical).

FINAL REMARKS

As recently highlighted in an editorial by Carrel and Hotaling (51), we as individuals and as a medical community providing care to infertility patients, including urologists, gynecologists, and IVF specialists, should ask whether we are providing the best care to our patients and the child yet to be born, by ignoring the health of the sperm. We must also confront the fact that ICSI is overused and the male factor is commonly overlooked. The financial incentives affecting the decision to bypass the male factor infertility through ICSI is not without adverse consequences. The existing data clearly indicate that sperm DNA damage is associated with reproductive health issues in the male and in the embryo. Thus, the use of sperm DNA testing is evidence-based and should be implemented by ART Clinics and doctors not yet using these assays. The primary objectives are to improve IUI and ART success, but more importantly, to improve the health of the father and resulting offspring.

Figure 1 - Proposed algorithm for planning intracytoplasmic sperm injection (ICSI) in cases of high sperm DNA fragmentation (SDF).



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AUTHORS' ROLES

SCE designed the manuscript, helped in data interpretation and coordination, and drafted the manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Schinfeld J, Sharara F, Morris R, Palermo GD, Rosenwaks Z, Seaman E, et al. Cap-Score™ prospectively predicts probability of pregnancy. Mol Reprod Dev. 2018;85:654-64.
2. Xu F, Zhu H, Zhu W, Fan L. Human sperm acrosomal status, acrosomal responsiveness, and acrosin are predictive of the outcomes of in vitro fertilization: A prospective cohort study. Reprod Biol. 2018;18:344-54.
3. Agarwal A, Arafa M, Chandrakumar R, Majzoub A, AlSaid S, Elbardisi H. A multicenter study to evaluate oxidative stress by oxidation-reduction potential, a reliable and reproducible method. Andrology. 2017;5:939-45.
4. Morris A, Siebert I, Agarwal A, Henkel R. Prediction of successful ICSI cycles by oxidation reduction potential (ORP) and sperm DNA fragmentation (SDF) analysis: a prospective study. European Society for Human Reproduction and Embryology (ESHRE) Annual Meeting, 2019;(O-016).
5. Majzoub A, Agarwal A, Cho CL, Esteves SC. Sperm DNA fragmentation testing: a cross sectional survey on current practices of fertility specialists. Transl Androl Urol. 2017;6(Suppl 4):S710-19.
6. Bungum M, Humaidan P, Axmon A, Spano M, Bungum L, Erenpreiss J, et al. Sperm DNA integrity assessment in prediction of assisted reproduction technology outcome. Hum Reprod. 2007;22:174-9.
7. Esteves SC, Gosálvez J, López-Fernández C, Núñez-Calonge R, Caballero P, et al. Diagnostic accuracy of sperm DNA degradation index (DDSi) as a potential noninvasive biomarker to identify men with varicocele-associated infertility. Int Urol Nephrol. 2015;47:1471-7.
8. Agarwal A, Parekh N, Panner Selvam MK, Henkel R, Shah R, Homa ST, et al. Male Oxidative Stress Infertility (MOSI): Proposed Terminology and Clinical Practice Guidelines for Management of Idiopathic Male Infertility. World J Mens Health. 2019;37:296-312.
9. McQueen DB, Zhang J, Robins JC. Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril. 2019;112:54-60. e3.
10. Spanò M, Bonde JP, Hjøllund HI, Kolstad HA, Cordelli E, Leter G. Sperm chromatin damage impairs human fertility. The Danish First Pregnancy Planner Study Team. Fertil Steril. 2000;73:43-50.
11. ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Nelen W, Peramo B, Quenby S, Vermeulen N, Goddijn M. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open. 2018;2018:hoy004.
12. Zini A. Are sperm chromatin and DNA defects relevant in the clinic? Syst Biol Reprod Med. 2011;57:78-85.
13. Zhao J, Zhang Q, Wang Y, Li Y. Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/ intracytoplasmic sperm injection: a systematic review and meta-analysis. Fertil Steril. 2014;102:998-1005.e8.
14. Simon L, Emery BR, Carrell DT. Review: Diagnosis and impact of sperm DNA alterations in assisted reproduction. Best Pract Res Clin Obstet Gynaecol. 2017;44:38-56.
15. Chen Q, Zhao JY, Xue X, Zhu GX. The association between sperm DNAfragmentation and reproductive outcomes following intrauterine insemination, a meta analysis. Reprod Toxicol. 2019;86:50-5.
16. Aitken RJ, Smith TB, Jobling MS, Baker MA, De Iuliis GN. Oxidative stress and male reproductive health. Asian J Androl. 2014;16:31-8.
17. Aitken RJ. DNA damage in human spermatozoa; important contributor to mutagenesis in the offspring. Transl Androl Urol. 2017;6(Suppl 4):S761-4.
18. Santi D, Spaggiari G, Simoni M. Sperm DNA fragmentation index as a promising predictive tool for male infertility diagnosis and treatment management - meta-analyses. Reprod Biomed Online. 2018;37:315-26.
19. Ribas-Maynou J, García-Peiró A, Fernández-Encinas A, Abad C, Amengual MJ, Prada E, et al. Comprehensive analysis of sperm DNA fragmentation by five different assays: TUNEL assay, SCSA, SCD test and alkaline and neutral Comet assay. Andrology. 2013;1:715-22.
20. Esteves SC, Santi D, Simoni M. An Update on Clinical and Surgical Interventions to Reduce Sperm DNA Fragmentation in Infertile Men. Andrology. 2019. [Epub ahead of print].

21. Agarwal A, Cho CL, Majzoub A, Esteves SC. The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility. Transl Androl Urol. 2017;6(Suppl 4):S720-33.
22. Lewis SEM. The place of sperm DNA fragmentation testing in current day fertility management. Middle East Fertil Soc J. 2013;18:78-82.
23. Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S, et al. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Hum Reprod. 2012;27:2908-17.
24. Esteves SC. Testicular versus ejaculated sperm should be used for intracytoplasmic sperm injection (ICSI) in cases of infertility associated with sperm DNA fragmentation | Opinion: Yes. Int Braz J Urol. 2018;44:667-75.
25. Muratori M, Tamburrino L, Marchiani S, Cambi M, Olivito B, Azzari C, et al. Investigation on the Origin of Sperm DNA Fragmentation: Role of Apoptosis, Immaturity and Oxidative Stress. Mol Med. 2015;21:109-22.
26. Esteves SC, Roque M, Bradley CK, Garrido N. Reproductive outcomes of testicular versus ejaculated sperm for intracytoplasmic sperm injection among men with high levels of DNA fragmentation in semen: systematic review and meta-analysis. Fertil Steril. 2017;108:456-67.
27. Lopes LS, Esteves SC. Testicular sperm for intracytoplasmic sperm injection in non-azoospermic men: a paradigm shift. Panminerva Med. 2019;61:178-86.
28. Belva F, De Schrijver F, Tournaye H, Liebaers I, Devroey P, Haentjens P, et al. Neonatal outcome of 724 children born after ICSI using non-ejaculated sperm. Hum Reprod. 2011;26:1752-8.
29. Esteves SC, Agarwal A. Reproductive outcomes, including neonatal data, following sperm injection in men with obstructive and nonobstructive azoospermia: case series and systematic review. Clinics (Sao Paulo). 2013;68(Suppl 1):141-50.
30. Esteves SC, Roque M, Bedoschi G, Haahr T, Humaidan P. Intracytoplasmic sperm injection for male infertility and consequences for offspring. Nat Rev Urol. 2018;15:535-62.
31. Cheung S, Schlegel PN, Rosenwaks Z, Palermo GD. Revisiting aneuploidy profile of surgically retrieved spermatozoa by whole exome sequencing molecular karyotype. PLoS One. 2019;14:e0210079.
32. Figueira R, Carvalho JF, Bento FC, Melo AA, Martinhago CD, Esteves SC. ICSI using surgically retrieved testicular sperm of non-azoospermic men with high sperm DNA fragmentation index and blastocyst ploidy: a safe approach. Abstracts of the 35th Annual Meeting of the European Society of Human Reproduction and Embryology, Hum Reprod. 2019;34 (Supp 1):i1–i543.
33. Esteves SC, Sharma RK, Gosálvez J, Agarwal A. A translational medicine appraisal of specialized andrology testing in unexplained male infertility. Int Urol Nephrol. 2014;46:1037-52.
34. Esteves SC. Interventions to Prevent Sperm DNA Damage Effects on Reproduction. Adv Exp Med Biol. 2019;1166:119-48.
35. Roque M, Esteves SC. Effect of varicocele repair on sperm DNA fragmentation: a review. Int Urol Nephrol. 2018;50:583-603.
36. Esteves SC. Should a Couple with Failed In Vitro Fertilization or Intracytoplasmic Sperm Injection and Elevated Sperm DNA Fragmentation Use Testicular Sperm for the Next Cycle? Eur Urol Focus. 2018;4:296-8.
37. Miyaoka R, Orosz JE, Achermann AP, Esteves SC. Methods of surgical sperm extraction and implications for assisted reproductive technology success. Panminerva Med. 2019;61:164-77.
38. Esteves SC, Prudencio C, Seol B, Verza S, Knoedler C, Agarwal A. Comparison of sperm retrieval and reproductive outcome in azoospermic men with testicular failure and obstructive azoospermia treated for infertility. Asian J Androl. 2014;16:602-6.
39. Esteves SC, Miyaoka R, Orosz JE, Agarwal A. An update on sperm retrieval techniques for azoospermic males. Clinics (Sao Paulo). 2013;68(Suppl 1):99-110.
40. Esteves SC, Miyaoka R, Agarwal A. Sperm retrieval techniques for assisted reproduction. Int Braz J Urol. 2011;37:570-83.
41. Esteves SC, Roque M. Extended indications for sperm retrieval: summary of current literature. F1000Res. 2019;8.
42. Esteves SC, Sánchez-Martín F, Sánchez-Martín P, Schneider DT, Gosálvez J. Comparison of reproductive outcome in oligozoospermic men with high sperm DNA fragmentation undergoing intracytoplasmic sperm injection with ejaculated and testicular sperm. Fertil Steril. 2015;104:1398-405.
43. Mehta A, Esteves SC, Schlegel PN, Niederberger CI, Sigman M, Zini A, et al. Use of testicular sperm in nonazoospermic males. Fertil Steril. 2018;109:981-7.
44. Sigman M. Testicular versus ejaculated sperm should be used for ntracytoplasmic sperm injection (ICSI) in cases of infertility associated with sperm DNA fragmentation | Opinion: No. Int Braz J Urol. 2018;44:676-9.
45. Esteves SC, Agarwal A, Cho CL, Majzoub A. A Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis on the clinical utility of sperm DNA fragmentation testing in specific male infertility scenarios. Transl Androl Urol. 2017;6(Suppl 4):S734-60.
46. Cho CL, Agarwal A, Majzoub A, Esteves SC. The correct interpretation of sperm DNA fragmentation test. Transl Androl Urol. 2017;6(Suppl 4):S621-3.
47. Majzoub A, Agarwal A, Esteves SC. Sperm DNA fragmentation: overcoming tandardization obstacles. Transl Androl Urol. 2017;6(Suppl 4):S422-4.
48. Cho CL, Agarwal A, Majzoub A, Esteves SC. A single cut-off value of sperm DNA fragmentation testing does not fit all. Transl Androl Urol. 2017;6(Suppl 4):S501-3.

49. Esteves SC, Agarwal A, Majzoub A. Sperm DNA fragmentation test results reflect the overall quality of the whole semen specimen. Transl Androl Urol. 2017;6(Suppl 4):S592-3.
50. Esteves SC, Majzoub A, Agarwal A. The importance of quality control and quality assurance in SDF testing. Transl Androl Urol. 2017 Sep;6(Suppl 4):S604-6.
51. Carrell DT, Hotaling J. Using sperm testing to improve patient and offspring health: rational, evidence-based care of the infertile male in the ART clinic. Transl Androl Urol. 2017;6(Suppl 4):S443-5.

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UPDATE IN UROLOGY

RECONSTRUCTIVE UROLOGY

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Editorial Comment: Dorsolateral fibromuscular tissue preservation during artificial urinary sphincter cuff placement is associated with low infection and erosion rates

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COMMENT

In this important paper Dr. Cheung and cols. from New York – USA, presented a modified technique of artificial urinary sphincter (AUS) placement with dorsolateral fibromuscular tissue of bulbo-spongiosus muscle (BSM) preservation.

The authors proposed a technique that is associated with low rates of erosion and infection in patients with high risk of complications (post radiotherapy, bladder neck contracture, metastatic prostate cancer). BSM, also known as the bulbo-cavernosus muscle, is a paired striated muscle originating from the perineal body and fixed in a median raphe involving the bulbar urethra (1, 2). BSM is related to the expulsion of seminal fluid and urine, especially the last drop, from the bulbar urethra by rhythmic contractions, acting as a pump to evacuate the contents of the bulbar urethra (3). During surgery, the authors performed a dorsal dissection of the urethra outside the BMS and made the inclusion of the dorsolateral fibromuscular tissue of the BMS in the cuff placement.

The authors concluded that the preservation of dorsolateral fibromuscular tissue of BMS during AUS placement is an effective means to achieve a low risk of erosion with good functional outcomes with low rates of re-operation and excellent long-term continence. The study is retrospective but the description of a 74% success index is amazing and this new technique with BSM preservation is very interesting.This article presents a good overview of the surgical treatment of erectile dysfunction-related Peyronie's disease, covering the best indication of the various possible surgical alternatives. To conclude, we also emphasize that pre-operative counseling about the realistic outcomes of surgery in PD is mandatory to achieve adequate postoperative satisfaction rates.

REFERENCES

1. Shafik A, El-Sibai O. Mechanism of ejection during ejaculation: identification of a urethra-cavernosus reflex. Arch Androl. 2000;44:77-83.
2. Yang CC, Bradley WE. Reflex innervation of the bulbo-cavernosus muscle. BJU Int. 2000;85:857-63.
3. Puppo V, Puppo G. Comprehensive review of the anatomy and physiology of male ejaculation: Premature ejaculation is not a disease. Clin Anat. 2016;29:111-9.

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UPDATE IN UROLOGY

RECONSTRUCTIVE UROLOGY

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Editorial Comment: Management of post TURP strictures

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COMMENT

Trans-urethral prostate resection (TURP) is one of the most common urologic surgeries and the urethral stricture is an important complication (1). In the present paper Dr. Kulkarni, in a prospective study with 170 patients shows that bulbar stricture is the most frequent affected area with stricture post TURP (143 patients) and that buccal mucosa graft (BMG) is safe, feasible and with long-term success in these patients that should be strongly considered. The overall success rate of Kulkarni with BMG was 82% in this paper. Other important presented result is that the Ventral approach is best suited for proximal bulbar strictures close to membranous urethra.

BMG placement can be ventral, dorsal or lateral (2-4). Ventral location provides the advantages of ease of exposure and good vascular supply by avoiding circumferential rotation of the urethra (5) and this paper shows that in post TURP stricture near the membranous urethra this technique is the best option. This is a very important publishing and we would like to congratulate the authors.

REFERENCES

1. Payne SR, Fowler S, Mundy AR. Analysis of a 7-year national online audit of the management of open reconstructive urethral surgery in men. BJU Int. 2019 Aug 16. [Epub ahead of print].
2. Prakash G, Singh BP, Sinha RJ, Jhanwar A, Sankhwar S. Is circumferential urethral mobilization an overdo? A prospective outcome analysis of dorsal onlay and dorso - lateral onlay BMGU for anterior urethral strictures. Int Braz J Urol. 2018;44:323-9.
3. Favorito LA, Conte PP, Sobrinho UG, Martins RG, Accioly T. Double inlay plus ventral onlay buccal mucosa graft for simultaneous penile and bulbar urethral stricture. Int Braz J Urol. 2018;44:838-9.
4. Alsagheer GA, Fathi A, Abdel-Kader MS, Hasan AM, Mohamed O, Mahmoud O, Abolyosr A. Management of long segment anterior urethral stricture (≥ 8cm) using buccal mucosal (BM) graft and penile skin (PS) flap: outcome and predictors of failure. Int Braz J Urol. 2018;44:163-71.
5. Barbagli G, Palminteri E, Guazzoni G, Montorsi F, Turini D, Lazzeri M. Bulbar urethroplasty using buccal mucosa grafts placed on the ventral, dorsal or lateral surface of the urethra: are results affected by the surgical technique? J Urol. 2005;174:955-7; discussion 957-8.

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UPDATE IN UROLOGY

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Editorial Comment: Female urethroplasty: contemporary thinking

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COMMENT

In this interesting review West and Lawrence show important points about a major and poorly studied topic: the female urethral stricture. In the review the authors show the management options and observed that multiple open urethroplasty techniques are described with various grafts and flaps, with good medium-term success. Minimally invasive techniques remain well-employed but have poor long-term success, with increased failure with multiple attempts at treatment and concluded that the use of vaginal flaps and buccal mucosal graft present interesting success rates and urethral dilation should be avoided due to disappointing long-term results.

An important topic to be discussed is what is the best option for surgical reconstruction of female urethral strictures with buccal mucosa graft? Ventral or dorsal approach? What is the best choice? Both dorsal and ventral approaches are acceptable options for the surgical reconstruction of female urethral strictures (1). Dr. Nayak in an interesting paper show that ventral-inlay buccal mucosal graft urethroplasty is a simple and safe method of urethroplasty in women with good results (2). In other interesting paper Dr Manasa shows that early functional results after dorsal onlay vaginal graft urethroplasty are good without any negative impact on continence or sexual functions. The dorsal buccal mucosa grafts have gained popularity, because they maintain intact the ventro-lateral urethral supporting structures, important for continence (3). In an interesting paper by Gomez et al, the authors show a success rate of the dorsal graft of 86% of the patients in a long follow-up with low morbidity (3). In this unusual disease, the use of buccal mucosa graft for treatment seems to be the best choice.

REFERENCES

1. Nayak P, Mandal S, Das M. Ventral-inlay buccal mucosal graft urethroplasty for female urethral stricture. Indian J Urol. 2019;35:273-277.
2. Manasa T, Khattar N, Tripathi M, Varshney A, Goel H, Sood R. Dorsal onlay graft urethroplasty for female urethral stricture improves sexual function: Short-term results of a prospective study using vaginal graft. Indian J Urol. 2019;35:267-72.
3. Gomez RG, Segura FJ, Saavedra A, Campos RA. Female urethral reconstruction: dorsal buccal mucosa graft onlay. World J Urol. 2019 Sep 21. [Epub ahead of print].

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Editorial Comment: Surgical Management of Peyronie's Disease With Co-Existent Erectile Dysfunction

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Peyronie's disease (PD) is a connective tissue disorder with fibrotic plaque in the tunica albuginea, leading to penile deformity (1). For years, we sought to find a better form of treatment, from experimental studies in basic sciences to the present day with consolidated surgical modalities (2). As we know, a large number of patients have erectile dysfunction (ED) associated with Peyronie's disease. In most guidelines it is well established that penile prosthesis (PP) implantation is reserved for treatment of PD in patients with ED, especially when they are non-responders to oral therapy (3). In this scenario, the goal of PD surgery is to achieve a functionally straight penis (curvature <20 degrees) with good erection (4).

In this interesting paper, a systematic search on PubMed online database was done using the MeSH terms "Peyronie's disease" and "erectile dysfunction" with the objective to highlight the results of penile prosthesis to correct refractory erectile dysfunction in patients with PD.

One of the interesting aspects brought in the paper refers to the ideal moment of surgery. The authors observed that the ideal time is after three months of stable curvature or after 12 months from the onset of symptoms. Another important aspect is the type of prosthesis that should be used. The author provided data from a multicentric study involving 166 men evaluated on the significant difference in satisfaction and complication rates between the malleable penile prosthesis (MPP) and the Inflatable Penile Prosthesis (IPP) groups. Residual curvature was present in 6% of the patients with MPP and 16.7% with IPP with no statistical significance (5). According to the European Guidelines of Urology a small risk of urethral perforation (3%) has been reported in patients with 'modeling' over the inflated prosthesis (6). Although IPP is most preferred, there is no good level of evidence to prove that IPP is better than MPP. In regard to secondary procedures, such as manual modeling, plication, or graft placement, no new data was observed differing from the current guidelines. Grafts are usually preferred when penile curvature is more than 60 degrees. There is no ideal graft and the selection of a particular graft depends on the local availability, cost, and surgeon's expertise. At the end of the paper the authors propose an algorithm for the surgical cor-

rection of Peyronie's disease with coexisting erectile dysfunction. In this algorithm, after penile prosthesis implantation, manual modeling should be performed when residual curvature higher than 30º is observed. Tunica incisions or plication should be performed if persistent curvature after modeling is present. Plaque incision / excision and grafting should be done for persistent curvature (even after releasing incisions) or if defect longer than 2 cm is present.

This article presents a good overview of the surgical treatment of erectile dysfunction-related Peyronie's disease, covering the best indication of the various possible surgical alternatives. To conclude, we also emphasize that pre-operative counseling about the realistic outcomes of surgery in PD is mandatory to achieve adequate postoperative satisfaction rates.

REFERENCES

1. Hatzimouratidis K, Eardley I, Giuliano F, et al. EAU Guidelines: Male Sexual Dysfunction.
2. Salehipour M, Izadpanah K, Safaei A, Kamranpoor M, Farsiani MR. Int Braz J Urol. 2014.
3. Carrieri, M.P., et al. A case-control study on risk factors for Peyronie's disease. J Clin Epidemiol, 1998. 51: 511.
4. Wilson, S.K. Surgical techniques: modeling technique for penile curvature. J Sex Med,2007. 4: 231.
5. HabousM, TealabA,FaragM,etal. Malleable penile implantis an effective therapeutic option in men with Peyronie's disease and erectile dysfunction. Sex Med 2018;6:24-29.
6. Wilson, S.K., et al. A new treatment for Peyronie's disease: modeling the penis over an inflatable penile prosthesis. J Urol, 1994. 152: 1121.

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Editorial Comment: Comparative Cost-effectiveness of Surgery, *Collagenase Clostridium Histolyticum*, and Penile Traction Therapy in Men with Peyronie's Disease in an Era of Effective Clinical Treatment

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COMMENTS

Peyronie's Disease has prevalence rates of 0.4-9%, with a higher prevalence in patients with ED and diabetes (1). We know that surgery has been considered the gold standard treatment of Peyronie´s disease. In most countries we have found that conservative treatment has poor acceptability especially in patients with greater curvature (2-4). However, as we know, the cost of surgery is high, so that patients who do not have access or do not want this treatment have few or no alternatives. In this scenario, the comparison of cost effectiveness between conservative and surgical treatments gains importance and this is the subject of this interesting article.

In this paper, Dr Kevin Wymer and his colleagues from Mayo Clinic, compared the cost effectiveness of treatment with collagenase Clostridium Histolyticum (CCH), traction therapy (RXPTT- a novel penile traction therapy device) and surgery. To evaluate effectiveness, parameters such as an improvement of >20% in penile curvature, complications for each of the treatments and quality of life parameters were considered. After comparison and statistical analysis, he noted that because of the high cost of surgery, with higher complication rates such as erectile dysfunction as well as the high cost of CCH with some local complications (penile ecchymosis, penile hematoma), the total cost for providing the same increase in quality of life was smaller with the use the RXPTT, demonstrating that this non-surgical device appears to have place in the treatment of Peyronie's disease.

Some limitations were highlighted by the author. The success criteria were 20% curvature improvement without considering other aspects such as the final penile length. Another important point is the patient's expectation. If a patient's primary goal was to achieve a fully straight penis, surgery would

be the most cost-effective option. In contrast, if length and preservation of erectile function were the primary objective, RXPTT would be preferred.

Some other aspects deserve to be mentioned. First, traction devices require treatment for a few hours during the day for a long period of time which decreases treatment adherence (5). Second, the choice of CCH as a comparison treatment: despite its proven effectiveness, we know it has a high cost (mean cost per patient = $ 33,628 at 10 years treatment) thus obviously disadvantaging in a cost effectiveness study. Also, other therapies such as injectable interferon, verapamil, oral pills and even vacuum devices should have been considered in the study. Finally, a point that needs to be commented even though noting that the study has been approved by the Mayo Clinic Conflict of Interest Board, is the fact that one of the authors of the paper is the developer of RXPTT, the device used in the study.

To conclude, we have here an unprecedented study on cost-effectiveness in Peyronie's disease, performed with methodological rigor, comparing three possible treatment modalities and which presents a new device for non-surgical treatment of this disease.

REFERENCES

1. Arafa M, Eid H, El-Badry A, Ezz-Eldine K, Shamloul R. The prevalence of Peyronie's disease in diabetic patients with erectile dysfunction. Int J Impot Res. 2007;19:213-7.
2. Da Ros CT, Graziottin TM, Ribeiro E, Averbeck MA. Long-term follow-up of penile curvature correction utilizing autologous albugineal crural graft. Int Braz J Urol. 2012;38:242-7; discussion 248-9.
3. Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2010;7:3572-88.
4. Kendirci M, Hellstrom WJ. Critical analysis of surgery for Peyronie's disease. Curr Opin Urol. 2004;14:381-8.
5. Hellstrom WJ, Montague DK, Moncada I, Carson C, Minhas S, Faria G, et al. Implants, mechanical devices, and vascular surgery for erectile dysfunction. J Sex Med. 2010;7(1 Pt 2):501-23.

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Editorial Comment: Low-Intensity Shock Wave Therapy in Sexual Medicine-Clinical Recommendations

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COMMENTS

In recent times, low-intensity shockwave therapy (LISWT) has become one of the therapeutic modalities for the treatment of andrological disorders with controversial findings, which makes it difficult to recommend them in the guidelines (1-3). In this scenario this interesting paper aimed to evaluate the applicability of the LISWT in the treatment of erectile dysfunction (ED), Peyronie's disease (PD) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

During their review, the authors analyzed 11 RCTs and 5 meta-analyzes that investigated LISWT for ED, 4 RCTs and 1 meta-analysis for PD and 5 RCTs for CP / CPPS. For erectile dysfunction purposes, although there is a tendency in this direction, the review made clear a heterogeneity among treatment protocols, with controversial findings and indication being restricted to vasculogenic ED. Before starting treatment, patients should be aware that the scientific evidence is controversial and that the expected improvement may not be clinically relevant. In relation to PD, data available from RCTs is poor. Patient inclusion criteria vary from stable disease to non-stable disease and follow-up assessment varies too much (24 weeks to 1 year) using different sources of energy and heterogeneous protocols proposed, making any comparison difficult. Nevertheless, in a large prospective, randomized, double-blind, placebo-controlled study, with four weekly treatment sessions of ESWT, they observed a significant improvement in penile pain and thus

LISWT could be an option for this purpose (4, 5). However, patients should be counseled that no effect can be expected on curvature and plaque size. In the same direction we have the results obtained for the CP/CPPS. There is no evidence for maintenance of the improvement over time. LISWT could be applied in patients with CP / CPPS, especially to non-responders to conventional therapies but again, patients should be advised about the lack of robust evidence with long- term shockwave therapy.

Despite the great enthusiasm and effort to demonstrate LISWT effectiveness in treating ED, PD and CP/CPPS, data over time are not robust and several uncertainties like if it is indeed an effective treatment, what is the best protocol to ensure a higher probability of treatment success and how long does the effect last, still persist. We are on the way, but no doubt future studies are still needed to address these questions.

REFERENCES

1. Müller A, Mulhall JP. Peyronie's disease intervention trials: methodological challenges and issues. J Sex Med. 2009;6:848-61.
2. Ralph D, Gonzalez-Cadavid N, Mirone V, Perovic S, Sohn M, Usta M, et al. The management of Peyronie's disease: evidence-based 2010 guidelines. J Sex Med. 2010;7:2359-74.
3. Gruenwald I, Kitrey ND, Appel B, Vardi Y. Low-Intensity Extracorporeal Shock Wave Therapy in Vascular Disease and Erectile Dysfunction: Theory and Outcomes. Sex Med Rev. 2013;1:83-90.
4. Palmieri A, Imbimbo C, Longo N, Fusco F, Verze P, Mangiapia F, et al. A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. Eur Urol. 2009;56:363-9.
5. Gao L, Qian S, Tang Z, Li J, Yuan J. A meta-analysis of extracorporeal shock wave therapy for Peyronie's disease. Int J Impot Res. 2016;28:161-6.

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Obstructive uropathy secondary to ureteral inguinoscrotal hernia

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CASE PRESENTATION

An 83-year-old male patient with a medical history of benign prostate hyperplasia was admitted with left inguinoscrotal pain and swelling. Physical exam revealed a large left-sided irreducible inguinoscrotal hernia (ISH). A non-contrast abdominopelvic computer tomography showed a left hydroureteronephrosis with a dilated ureter included in a paraperitoneal ISH associated with left nephroptosis. Renal function was normal, with a creatinine level of 0.92mg/dl.

Subsequent surgical repair by hernioplasty with a synthetic mesh placement was performed in a multidisciplinary approach. Intraoperatively, we found a large paraperitoneal ureteral ISH with dilated gonadal vessels. Patient was discharged after 3 days without complications. The patient is free of symptoms after 3 months of follow-up and the IVU showed hydroureteronephrosis resolution.

DISCUSSION

Inguinoscrotal herniation (ISH) of the ureter is extremely rare, even more on native kidneys (1). ISH is common in 50-60 years old men and frequently associated with pelvic kidney (2). We can find both paraperitoneal (80%) and extraperitoneal presentation (20%) (3). Paraperitoneal type has a peritoneal indirect sac that pulls the ureter through the defect, forming part of the hernia wall, due to a layer of posterior peritoneum. Extraperitoneal type is characterized by containing no peritoneal sac and the ureter is involved alone or with retroperitoneal fat (3).

Figure 1 - A) Coronal abdominal non-contrast-enhanced CT scan showing dilated left pelvic kidney (asterisk) and dilated ureter (arrow) in the inguinal hernia. B) Axial non-contrast-enhanced CT scan with loop of the left ureter in the hernia (arrow). C) Sagittal non-contrast-enhanced CT scan with ureteral inguinoscrotal hernia (arrow). D) Identification of left ureter (arrow) during the inguinal hernia repair.

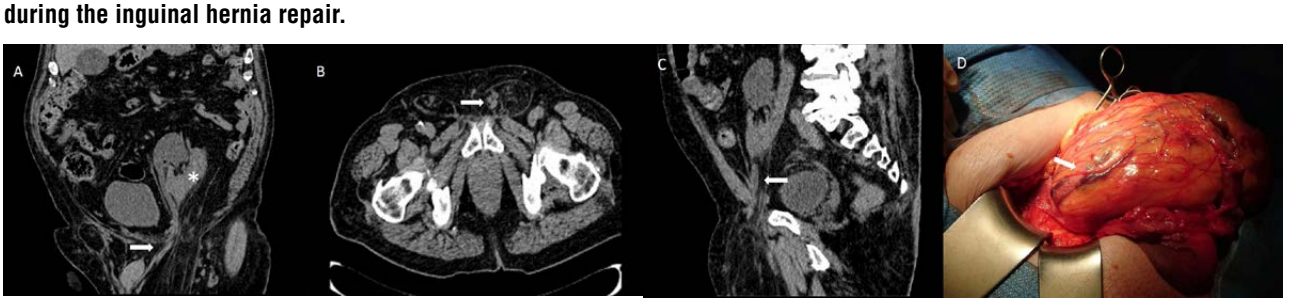
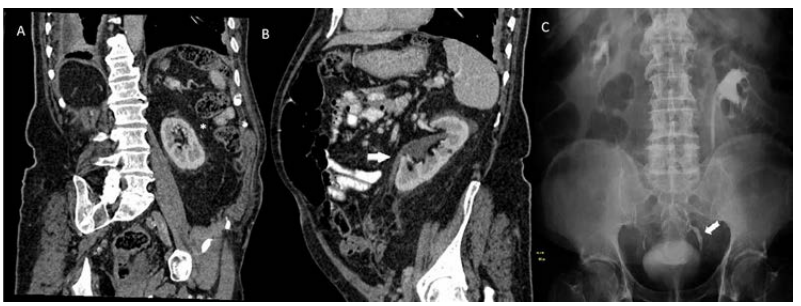


Figure 2 - A) Coronal-oblique post-contrast-enhanced abdominal CT scan showing left pelvic kidney (asterisk) without dilated ureter after correction of the inguinal hernia. B) Sagittal CT scan showing non dilated left pelvic kidney (arrow). C) Intravenous pyelogram post hernioplasty.



This condition usually has an asymptomatic course unless ureteral obstruction causes pain, infections or renal dysfunction (1, 3), signs that indicate ISH should be considered. Computed tomography scan helps to delineate the course of the ureter (3). Treatment modalities consist of surgical repair (1-3).

CONFLICTS OF INTEREST

None declared

REFERENCES

1. Sidiqi MM, Menezes G. Asymptomatic herniation of ureter in the routine inguinal hernia: A dangerous trap for general surgeons. Int J Surg Case Rep. 2018;49:244-6.
2. Dikmen AV, Guneri C, Yalcin S, Acikgoz O, Ak E, Cetiner S. A Ureteral Inguinoscrotal Hernia from a Pelvic Kidney. Curr Urol. 2017;11:51-3.
3. Yahya Z, Al-Habbal Y, Hassen S. Ureteral inguinal hernia: an uncommon trap for general surgeons. BMJ Case Rep. 2017;2017.

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Analysis of surgeon biometrics during open and robotic radical cystectomy with electromyography and motion capture analysis

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ABSTRACT

Purpose: To determine feasibility of measuring surgeon physical stress during both open radical cystectomy (ORC) and robotic radical cystectomy (RRC).

Materials and Methods: One patient underwent ORC, while the other underwent RRC by a single surgeon. The diversion was excluded from this study. Noraxon® myoMOTION™ kinematics sensors were used to quantify the amount of joint and segmental motion of the spine, shoulders, and head. myoMUSCLE™ EMG sensors were used to measure activation levels, patterns, and fatigue characteristics of key muscle groups. The Prone Static Plank Test (PSPT) and Modified Biering-Sorensen Test (MBST) were used to assess surgeon strength and endurance of core musculature.

Results: The surgeries were represented in five stages. During ORC, the percentage of time spent in cervical flexion was 98%, 91.8%, 87.5%, 100%, and 97.1%, respectively. During RRC, 100% of the time was spent in cervical flexion. Activation of key muscle groups was examined across all stages and expressed as a percentage of peak activation. MBST times were both 25 second pre-and post-surgery ORC and 25.1 seconds pre-surgery and 32.4 seconds post-surgery for RRC. PSPT times were 68 second pre-surgery and 48 seconds post-surgery for ORC, and 59 second pre-surgery and 51 seconds post-surgery for RRC.

Conclusion: We were able to identify meaningful data using kinematic and EMG analysis during ORC and RRC. We were able to identify target muscle groups that will be used to conduct a larger study with multiple surgeons to help determine if there is an ergonomic advantage to RRC over traditional ORC.

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VIDEO SECTION

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Apical sling for laparoscopic sacrohisteropexy in a young virgin patient with joint hypermobility syndrome

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ABSTRACT

Introduction: We are faced with a young patient with uterine prolapse and urinary difficulties due to Joint Hypermobility Syndrome, a congenital collagen disease that predisposes woman to the development of pelvic organ prolapse. The patient had urinary difficulty requiring standing and bowing to reduce prolapse and then start urination. This video demonstrates that videolaparoscopic technique is feasible for the treatment of uterine prolapse in young and sexually virgin woman.

Materials and Methods: We separated the bladder from vagina and opened the peritoneum anterior to the uterus. Next, we attached the sigmoid colon to the left abdominal wall in order to better expose the promontory. We then opened the peritoneum posterior to the uterus and medially tunnelled the right uterosacral ligament, transfixing the broad ligament and passing the end of a polypropylene mesh through this tunnel to the posterior region of the uterus. The same maneuver was performed on the other side so that the mesh surrounded the anterior portion of the cervix while its two extremities were posterior to the uterus. The mesh was fixed on the anterior surface of the uterine cervix and its two extremities were fixed to the promontory in the anterior longitudinal ligament of the spine. Finally, we closed the peritoneum.

Results: Uterine prolapse was corrected, with good recovery.

Conclusions: Videolaparoscopic technique is feasible for correction of uterine prolapse, being effective and safe in virgin woman.

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VIDEO SECTION

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Robotic excision of deep infiltrating endometriosis at the uretero-vesical junction

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ABSTRACT

Objective: To describe the surgical approach for Deep Infiltrating Endometriosis (DIE) of the uretero-vesical junction and bladder reconstruction.
Materials and methods: Bimodal visualization with the help of cystoscopy and robotic-assisted laparoscopy is a useful technique that can be used to delineate the deep infiltrating endometriotic lesion of the bladder wall.
Results: We present the case of a 36 year old G3P3 woman, with right sided hydroureter/hydronephrosis and biopsy proven DIE. Pre-operative MRI was suggestive of bladder wall lesion involving the posterior right bladder wall and extending to right uretero-vesical junction. On entry into the abdomen, the pelvis looked normal except for the right sided hydroureter. Hysterectomy was performed without difficulty. Bimodal visualization was then utilized to delineate the endometriotic lesion. Cystotomy was then performed and endometriotic lesion of the bladder was subsequently excised. This was followed by right sided ureterolysis and excision of endometriotic lesion of uretero-vesical junction. Bladder was reconstructed and the ureter was re-implanted. Psoas hitch was performed to reduce tension on the anastomosis. Post-operative course was uneventful. Retrograde cystogram performed one month post-operatively showed no contrast leak after re-implantation of right ureter. Foleys catheter was removed at 4 weeks post-operatively. Ureteric stent and nephrostomy tube were removed post-operatively at 8 weeks and 9 weeks respectively.
Conclusion: Deep infiltrating endometriosis can be present in normal looking pelvis. In patients with deep infiltrating endometriosis of the bladder, bimodal visualization might be needed to delineate the extent of the disease.

CONFLICT OF INTEREST

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VIDEO SECTION

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Laparoscopic ureteroplasty with buccal mucosa graft for long proximal ureteral stenosis: A step by step video

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ABSTRACT

Introduction: Strictures of the proximal ureter may occur from iatrogenic injury or impacted kidney stones. Many methods of surgical correction have been described, but the current treatment options can have significant morbidity associated with bowel substitution and vascular complications. Buccal mucosa grafting (BMG) has revolutionized the management of urethral strictures, but has not gained widespread use for ureteroplasties. Naude first described the use of BMG in the open repair of ureteral strictures, but only recently new techniques with minimally invasive approaches are being described.

Objective: To show in this video the step-by-step of a laparoscopic inlay ureteroplasty with buccal mucosa grafting of a 75-year-old male with a long left proximal ureteral stricture secondary to previous ureteroscopies.

Patient and Methods: A healthy 75-year-old male with history of two previous ureteroscopies for impacted left proximal ureteral stones, presented with left lumbar pain. Urinary ultrasound and computed tomography showed left hydronephrosis. Pyelography revealed a long left proximal ureteral stenosis. The patient was submitted to a laparoscopic ureteroplasty with BMG after incision of the anterior aspect of the stenotic ureteral segment. The surgery was 120 minutes long, with no complications. The patient was discharged on second post-operative day and the ureteral stent was removed after 4 weeks, with a clinical and radiological success.

Conclusion: This technique is an excellent option that has been described recently, with low morbidity and good results. It offers the possibility of resolving long proximal ureteral strictures precluding the need for more extensive and morbid surgeries.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic-assisted surgical removal of retroperitoneal schwannoma by transmesocolic access

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ABSTRACT

Introduction: Schwannoma are usually benign tumors, most of the cases are asymptomatic, and others may present symptoms by compression. In the literature robotic surgery were described in 8 cases. We emphasize that robotic surgery improves visualization and enable the performance of this procedure.
Objectives: Describe and evaluate the results and benefits of resection of a retroperitoneal tumor by means of robotic surgery by transmesocolic access.
Materials and methods: We present a case of a 34 year old patient, with low back pain, who were diagnosed with a retroperitoneal tumor in which an incisional biopsy by laparoscopy was previously performed with the diagnosis of schwannoma, measuring 4.1cm x 3 cm next to the left renal hilum and near to abdominal aorta. Robotic surgery was performed. It was possible to localize the vena cava, aorta and left renal hilum and consequently it was possible to preserve the adjacent structures. The resection of the tumor was carried out carefully allowing complete tumor resection.
Results: The total of procedure time was 230 minutes, blood loss was 60ml, 1 day of hospital stay without complications. The histopathological findings confirmed benign Schwannoma.
Conclusion: The maximization of robotic surgery images offers dexterity and dissection capacity, required for the complex dissection of masses in the retroperitoneum. It is safe and effective for removing benign retroperitoneal schwannomas when performed by experienced surgeons. This transmesocolic robotic assisted surgical approach could be an option in selected cases.

CONFLICT OF INTEREST

None declared.

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