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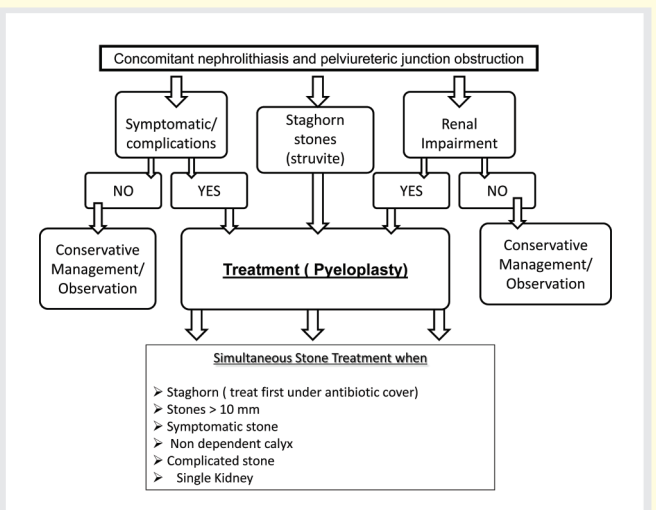

Figure 1 - Suggested algorithm for the management of established PUJO and concomitant nephrolithiasis. (Page 16)

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EDITORIAL
IN THIS ISSUE

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Urethral stricture: the oldest urologic disease in 2017

The January-February 2017 issue of the International Braz J Urol presents original contributions with a lot of interesting papers in different fields: Female Urinary Incontinence, Male Urinary Incontinence, Bladder Cancer, Pelvic-Ureteric Junction Stenosis, BPH, Prostate Cancer, Bladder Cancer, Renal Cancer, Testicular Cancer, Penile Cancer, Overactive Bladder Syndrome, Ureteral Obstruction, Pediatric Urology, Interstitial Cystitis and Urethral Stricture. The papers come from many different countries such as Brazil, USA, Turkey, Italy, Belgium, India, China, United Kingdon, Portugal, Taiwan and Serbia, and as usual the editor's comment highlights some papers. We decided to comment 2 papers about a very usual and challenging topic in urologic practice: The Urethral Stricture.

Doctors Pandian and collegues, from India performed on page 125 an interesting study about the Pre-operative evaluation of pelvic fracture urethral distraction defect by MRI. The authors performed a prospective study with 20 patients with pelvic fracture and urethral distraction using IIEF questionnaire to study the erectile funtion, retrograde urethrogram and micturating cystourethrogram (RGU+MCU) and MRI pelvis and concluded that MRI did not offer signicant advantage over MCU in the subgroup of men with normal erections. The cavernosal injury noted on MRI strongly correlated with ED. Role of MRI may be limited to the subgroup with ED or an inconclusive MCU.

Doctor Kanodia and collegues from India too, described on page 161 an interesting challenging clinical case about a Intraoperative breakage of Sachse's knife blade during a internal urethrotomy and managed with the help of double J stent removing forceps. The authors concluded that this complication should be kept in mind and instruments should be checked properly by the operative surgeon prior to start the procedure. Retained sharp objects like knife blade in urethra as a result of breakage of Sachse's knife blade can be managed endoscopically.

Urethroplasty is a procedure that has a high success rate but exists a small group of patients with the chance of multiple interventions: Urethal dilatation, Internal urethrotomy and re-do uretrhoplasty (1). The Internal urethrotomy (IU) has the advantages of an easy, simplicity, speedy and shorty convalescence in treatment of urethral stricture (2). Complications of IU are usually minor, including infection and hemorrhage. Previous studies comparing the IU with the urethroplasty shows that the IU requires further surgery or continued self-dilatation compared with urethroplasty (3, 4). In this number of Int Braz J Urol we observed a rare complication of IU: The breakage of the cold knife and this manipulation by endoscopy. This kind of complication needs to be kept in mind during the IU.

Pelvic fracture urethral distraction defect (PFUDD) may be associated with disabling complications, such as recurrent stricture, urinary incontinence, and the most

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common complication associated with this condition, the erectile dysfunction (5). In this number of Int Braz J Urol we observed a paper that compare the MRI and VCUG, with the prediction of erectile dysfunction in PFUDD. The three-dimensional imaging modalities provide more comprehensive information regarding the anatomy of urethral diseases (6), but in this preliminary report the MRI do not replace the VCUG in the prediction of erectile dysfuntion.

In this new year of 2017 we are still discussing surgical techniques and diagnostic methods of one of the oldest pathologies known to the urologist. The urethral stricture remains a challenging pathology today.

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EDITORIAL

The creation, development and diffusion of the LARCG- latin american renal cancer group

Stênio de Cássio Zequi [1], Diego Abreu Clavijo [2] and all other LARCG* Members**

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INTRODUCTION

As usually verified in many malignancies, the majority of the scientific information about renal cell carcinoma (RCC) is produced in developed countries mainly in North America and Europe. This knowledge is derived from great casuistries, joined in multi-institutional collaborative study groups or in International diseases consortiums.

Consistent epidemiologic and scientific data originated in the Latin America (LA) are lacking. LA is a large subcontinent, composed by more than 20 countries (much of them great economies), encompassing around 640 million habitants. Latin American population ethnicity is unique, due to an intense miscegenation, differing from northern hemispheric populations. The LA's population was composed by several civilizations over the years: pre Colombians, (Amerindians), black slaves descendant's (distinct groups of the African slaves that were sent to North America and Caribe). The predominance of Europeans in LA corresponded to Iberians, and Italians, few French and Germans. We have few Anglo-Saxon, Scandinavian and Northern and Eastern Europeans. Regarding Middle East and Africans, the more prevalent immigrants were Syrian, Lebaneses, Jewishs and few Armenians. Also, there are few Arabic, Persian and North African populations. From Asia, the predominance has been established by Japanese and in the last decades, by some Korean and Chinese. There is almost no people from South Asia, Oceania and Pacific Islands etc., differing from US, for example. The LA racial miscegenation resulted in particular genetic groups such as Mulattoes, Mestizos, Zambos, Cimarron's, Cafuzzos, mamelucos etc (1, 2). In the era of molecular biology, and "omics", it seems amazing to know the demographic, clinical, pathological and biomolecular profiles of several cancers in different populations. The research opportunities in these LA populations are exciting.

However, the socioeconomic level and the human development index among LA's populations in general are under than desired. Health care systems in our subcontinent are heterogeneous, being possible to find in a same country (or in a same city), side by side, the more developed, and the more precarious medical services. Additionally, the Latin American Institutions, and its practitioners are not skilled in participating in multicenter collaborative study groups. The language may constitute an additional barrier, since the number of non-native English speakers (and writers) is large. At the same time, the background and the funds available to incentivize scientific productions are insufficient, in contrast with several primary and more urgent health requirements in LA.

The LARCG

In face of this scenario, in May 2013, during the 108th American Urological Society Annual Meeting in San Diego, colleagues from Brazil (SCZ) and Uruguay (DAC), decided to create an international, multicenter, nonprofit, collaborative study group, focused on kidney cancer, named LARCG (Latin American Renal Cancer Group).

The main generic role of LARCG is to promote knowledge and the research development regarding renal cell carcinoma (RCC) in LA. In order to reach this, it has become necessary to aggregate people and Institutions dedicated to this disease.

Aims and consolidation

Among the scopes of LARCG, the main ones were: 1) the creation of a great and multifaceted data bank with information of RCC in LA; 2) to stablish international scientific cooperation between the LARCG institutions and developed research centers or with collaborative uro-oncological intergroups; 3) to proportionate facilities that result in the production of high level scientific publications; 4) To stimulate the participation of LARCG members in worldwide recognized scientific meetings.

The first step to concretize our aims was to invite LA's key opinion leaders, to participate, and we had a quick and massive adhesion (special thanks to the work developed by Dr. Alejandro Nolazco, from Argentina in this task). On 2014, after a few months we had the adhesion of 24 institutions from six countries (Brazil, Uruguay, Argentina, Chile, Mexico and Spain), constituting the first round of the LARCG.

At the same time, through electronic assemblies, a statute was approved by all LARCG members. According to this agreement, it was created the Executive Directory, the Member's Council, and the Scientific and the Ethics Committees. In each participating center, an Urologist Leader (UL) was nominated.

The UL must diffuse the LARCG ideas on each center recruiting urologists, and designating expert uro--pathologists, and clinical oncologists. These colleagues constitute the LARCG Pathol Branch and the LARCG Oncol Branch respectively, reinforcing the multidisciplinary characteristics of the group.

Today, LARCG is active, supported by annual fees paid by its members and is consolidated: www.larcg.org (3).

Scientific Steps

The first step in the scientific direction was the creation of an extensive data bank, containing 176 demographical, clinical, laboratorial and pathological variables, all of them previously codified and with careful protection of the patients' identifications. This data bank was sent to 24 institutions participants of the first round of the LARCG, in January 2014, and there were six months for the return of the information. At the end of 2014, we received information from 4280 RCC Patients. From these group, 3817 patients were eligible for a realization of the "*First epidemiological survey and an early survival analysis"*, form LARCG. These results were presented for the first time at the Main Session of the CAU - Confederacion Americana de Urologia Meeting, in Punta del Este Uruguay, in November, 2014. During this congress, it was realized the *First Annual LARCG Meeting*, with the presence of the majority of our members. Few months later, in 2015 April, these first analyses results, and the structural aspects of the LARCG, were presented at the "2015 Spring SWOG (Southwest Oncology Group) Meeting", in San Francisco, California. (thanks to the friendship of the SWOG, in the names of Drs. Ian M. Thompson, MD, Primo N. Lara MD, and Manuel Valdivieso, MD). After a few weeks, LARCG performed it's *Second Annual Meeting* during the 2015 AUA Annual Meeting in New Orleans LO, in a meeting room su-

pported by the AUA (special thanks to the personal collaboration performed by Shlomo Raz, MD).

LARCG promoted Scientific International Meetings in São Paulo, in March 2015, at AC Camargo Cancer Center, and in October, 2015, in the British Hospital in Buenos Aires.

In the end of 2015, the first LARCG season of submission of scientific projects was opened, and we received several applications, fourteen of them were approved by the Ethics and the Scientific Committees. All of these projects were presented during the *Third LARCG Annual Meeting*, realized in San Diego, during the 2016 AUA Meeting, under the support of the AUA. In this Section, we were proud to receive a special honored Guest, W. Marston Linehan, MD.

During the 2016 Meeting of the Associacion Argentina de Urologia, in Tucuman-Argentina), "Contemporary outcomes in the Management of Metastatic Renal Cell Carcinoma from the Latin American Renal Cancer Group (LARCG)" was presented (4). In October 2016, at the SIU - Societé Internationnale D' Urologie International Meeting in Buenos Aires, two abstracts were presented: one reporting the creation and development of the LARCG (5) and the other evaluating the Role of the American Society of Anesthesiology Classifications as a prognostic Factor in RCC (6).

The second Round: In 2015 LARCG finalized the adhesion of 45 centers, from Brazil, Uruguay, Argentina, Chile, Peru, Bolivia, Mexico and Spain. At this time, our Scientific Committee corrected and enhanced our data bank, and sent it to all centers, that had some months to fill it and/or to correct the previous imprecisions and return it to us. At the end of 2016, we finalized the second round, having information of 5223 patients (sent by 35 of our centers – there are 10 inactive centers, yet). The information is customized in a data bank. Now the specific variables's informations has been sent to the LARCG investigators which had aprooved research projetcs.

LARCG Pathologic Branch Activities

One of the most significant initiatives of the LARCG is to integrate the demographic, clinical data with pathological samples of each respective patient. For this task, we must acknowledge the non-interested collaboration of Dra. Isabela Werneck da Cunha, MD, PhD, (Leader of the LARCG Pathol), the LARCG Pathologists, and the personal contribution of Dr. George Netto, MD. Those skilled pathologists are centrally reviewing and reclassifying thousands of samples, according to the 2012, ISUP - International Society of Urological Pathology Consensus (7). From each case, samples of tissue microarray have been prepared (there were more than 750 samples of clear cell RCC from Brazil and Uruguay, already prepared). Argentinian Pathologists are reviewing their cases at this time. The junction of clinical, epidemiological data and pathological samples, for sure, will result in multiple opportunities for research and assays. In the future, biological fluids, frozen tissues etc. might be joined, under rigorous ethical and legal cares.

International Collaborations

There is a signed international agreement between two LARCG Centers (AC Camargo Cancer Center, Brazil and Pasteur Hospital, Uruguay) and Lee Moffitt Cancer Center, from Tampa, US, through Dr. Philippe P. Spiess, MD and Jorge Lockhart, MD.

Other collaborations has been stablishing with one of the SWOG's centers (University de California Davis-thanks to Dr. Primo Lara, MD) and AC Camargo Cancer Center. Some LARCG centers will collaborate with the recently aproveed project INCITO-INOTE (founded by Brazilian Offical fomment Agencies) 8, leadeared by VIlma Regina Martins, MSc, PhD.

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Plans for 2017 and beyond

For 2017, LARCG web site, originally in Spanish, will become bilingual, including the English idiom. Periodically, at our home page, newsletters, editorials, clinical cases discussions will be available.

The Next *LARCG Annual Meeting (4th)* will be held in Boston 2017, during the next AUA Annual Meeting. During this meeting, the research projects underway will be presented, and worldwide recognized RCC Speakers will be invited.

Negotiations are in course to establish future collaborations with international research groups and with RCC patient's protection and educational groups. We are now looking for a sponsor institution, that can support LARCG in its several and infrastructural logistics requirements.

We wish a bright 2017 for all LARCG members, collaborators and of course, for our patients.

***Coordinator**

Stênio de Cássio Zequi and Diego Abreu Clavijo

****Urologist leaders**

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DIFFERENCE OF OPINION

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Should routine neonatal circumcision be a police to prevent penile cancer? | *Opinion: Yes*

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Keywords: prevention and control [Subheading]; Circumcision, Male; Penile Neoplasms; Phimosis

This theme is controversial because no major medical organization recommends universal neonatal circumcision and no major medical organization calls for banning it either. The argument that this procedure must be kept within the purview of medical professionals is found across all major medical organizations. In addition, the organizations advise medical professionals to yield to some degree to parents' preferences, commonly based in cultural or religious views, in the decision to agree to circumcise (1). Circumcision may be used to treat pathological phimosis, refractory balanoposthitis and chronic, recurrent urinary tract infections (2, 3). Circumcision is contraindicated in infants with certain genital structure abnormalities, such as a misplaced urethral opening (as in hypospadias and epispadias), curvature of the head of the penis (chordee), or ambiguous genitalia, because the foreskin may be needed for reconstructive surgery. Circumcision is contraindicated in premature infants and those who are not clinically stable and in good health (3-5). If an individual, child or adult, is known to have or has a family history of serious bleeding disorders (hemophilia), it is recommended that the blood be checked for normal coagulation properties before the procedure is attempted (3, 5). A 2010 review of literature worldwide found circumcisions performed by medical providers to have a median complication rate of 1.5% for newborns and 6% for older children, with few cases of severe complications (6). Bleeding, infection and the removal of either too much or too little foreskin are the most common complications cited (6). Complication rates are higher when the procedure is performed by an inexperienced operator, in unsterile conditions, or when the child is at an older age (6). Circumcision does not appear to have a negative impact on sexual function (7).

The practice of neonatal circumcision exerts a protective factor avoiding the genesis of penile cancer. While the presence of phimosis is a strong risk factor for penile cancer, neonatal circumcision appears to be a protective factor (8, 9). The incidence of penile cancer in the Jewish population, where the practice of neonatal circumcision is universally practiced, approaches zero. There are only 9 reports of penile cancer in circumcised Jews in the neonatal period, reported in the world literature. Interestingly,

our group had the opportunity to treat an Israeli patient, of Jewish religion, who underwent neonatal circumcision and had an advanced penile tumor (10). The incidence rate of penile cancer in India where circumcision is not performed routinely, is 3.32 / 100,000 inhabitants, compared with rates close to zero found in Jews born in Israel. In countries of Muslim religion, where circumcision is performed in infancy, outside the neonatal period, there is an increase in the incidence of this neoplasia by up to 3 times (11). Several studies observed an increased risk for invasive penile cancer among men not circumcised in childhood (9, 12). The presence of a foreskin do not increase the risk on penile cancer however the presence of phimosis in men with penile carcinoma is high, ranging from 44% to 85% (8). Phimosis leads invariably to retention of smegma resulting in conditions of chronic irritation with or without bacterial inflammation of the prepuce and the glans. Smegma is a whitish film found under the foreskin of uncircumcised males. It contains bacteria, other microorganisms, dead skin cells, mucous, and other components. Smegma may cause chronic inflammation and recurrent infections that lead to preputial adhesions and phimosis. Substantial increased relative risk for penile cancer was recorded (up to 65-fold) among males with phimosis (8, 9).

Infection by high-risk HPV group is probably the major cause of anogenital cancers. High transmission potential with a low impact on herd immunity means extensive vaccination would be required to substantially reduce the incidence of cancer of the cervix and penis caused by high-risk HPV types. Further, vaccination of males against HPV appears to represent an expensive measure for prevention of penile cancer, particularly when one considers that high-risk HPV is present in only half of penile cancers. HPV vaccination of males should nevertheless help reduce cervical, anal and perhaps oropharyngeal cancers.

On the other hand, lack of circumcision is a risk factor for phimosis and balanitis which themselves are risk factors for penile cancer. This would explain why invasive penile cancer is rare in circumcised men

Circumcised men are consistently less likely than uncircumcised men to have HPV infection at the glans/corona and urethra. Several studies showed that male circumcision is associated with an overall reduction in the prevalence of genital HPV infection in men (13-16). These site-specific effects possibly occur because the foreskin provides a suitable environment around the glans for HPV infection (13) and HPV type-specific concordance has been shown between the glans/corona and foreskin in uncircumcised men that possibly reflects simultaneous infection or autoinoculation (17). Thereby, male circumcision reduces the risk of HPV infection among men and consequently reduces the exposure of women to high-risk HPV. It explains why women with circumcised partners are at lesser risk of cervical cancer. Hence, the observed evidence for a protective effect of male circumcision on cervical HPV infection has prompted the suggestion that male circumcision could be considered a major intervention measure to prevent the incidence of both diseases (18). IARC study (19) found strong epidemiological evidence that male circumcision is associated with a reduced risk of genital HPV infection in men and with a reduced risk of cervical cancer in women, notably among women with high-risk partners. Male circumcision may supplant HPV vaccines in protecting against other different genotypes of HPV and would be a tangible tool to reduce female genital infections.

In recent study, our group found HPV in 46.66% of our patients with phimosis, of whom 50% had high risk HPV genotypes. Of asymptomatic cases 16.36% were HPV positive but only 1 sample showed high risk HPV. We detected a significantly high rate of HPV genital infection in patients presenting with phimosis compared with asymptomatic men ($p=0.00167$). The prevalence of high risk HPV genotypes in patients with phimosis was also statistically significant ($p=0.0004$). We found a robust association between phimosis and the genital HPV prevalence in men and a significant frequency of high risk HPV. However, more studies are needed to adequately assess the effect of male circumcision on the acquisition and clearance of HPV infections. The focus of the treatment with vaccination or circumcision should be men in early age range (20). Taking into account the literature data and the limitations to perform the surgery, cited above, neonatal circumcision would be the best procedure to prevent penile cancer.

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DIFFERENCE OF OPINION

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Should routine neonatal circumcision be a policy to prevent penile cancer? | *Opinion: No*

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Routine neonatal circumcision remains a controversial topic. The most recent Canadian Paediatric Society does not recommend routine circumcision of every newborn male (1). And although prior statements from the American Academy of Pediatrics recommended against circumcision, the most recent recommendation states that circumcision outweigh the risk and the procedure's benefits justify it for families who want it (2). The benefits mentioned by the American Academy of Pediatrics included prevention of urinary tract infections, transmission of sexually transmitted infections, and penile cancer. Prevention of penile cancer may be related to increasing daily hygiene and decreasing sexually transmitted infections such as human papilloma virus (HPV) in circumcised males. However, with improvements in daily hygiene and sexually transmitted infection prevention strategies, neonatal circumcision may not be critical for the prevention of penile cancer, especially in western countries.

The association between lack of circumcision and penile cancer has been well documented (3). A meta-analysis found a strong protective effect of childhood circumcision on invasive penile cancer in 3 studies (OR 0.33; 95% 0.13-0.83) (3). However, in other studies when analyses were restricted to boys without a history of phimosis, the meta-analysis found that the protective effect of childhood circumcision on invasive disease no longer persisted (3). In addition, penile cancer continues to be one of the rarer malignancies in the world. In the United States where circumcision is prevalent, the rarity of disease is highlighted by its decreasing incidence. An analysis from the Surveillance, Epidemiology and End Results (SEER) database showed that the penile cancer incidence decreased to 0.58 per 100,000 in 1993-2002 from 0.84 per 100,000 in 1973-1982 in the United States (4). However, there is also a similar trend in countries with low circumcision rates such as Denmark and Finland (5, 6). In Denmark, penile cancer risk decreased from 1.15 per 100,000 in the 1940s to 0.82 per 100,000 in the late 1980s (5). Finland reported an incidence rate of 0.5 per 100,000 (6). Coupled with the rarity of penile cancer and conflicting evidence in the literature, it is hard to justify routine neonatal circumcision for all healthy males, including those without any preputial abnormalities, solely for the prevention of penile cancer.

Despite its rarity, there are several common factors that have been implicated to cause penile cancer. Factors resulting in phimosis, balanitis, and smegma have been associated with penile cancer in a meta-analysis (7). This has often been attributed to the

lack of circumcision and poor hygiene as a major risk factor in developing these inflammatory conditions. However, with improved daily hygiene, these conditions can still be combatted even with a lack of circumcision. For example, in the Denmark population where there is only a 2% circumcision rate, the incidence of penile cancer was shown to be steadily declining, likely coinciding with an increase in indoor bathrooms and improved hygiene (5). However, it's notable that the most recent study of the same population found an increasing rate of penile cancer from 1978 to 2008 (8). This study reported an average annual percentage change of 0.8% in incidence resulting in an increase in incidence to 1.3 per 100,000 men in 2008. Although this study did not contain data regarding HPV status, the prevalence of HPV in Denmark has also been found to be as high as 33-45% of men in several reports (9, 10). In addition, several studies have shown an increase in HPV-associated cancers in Denmark over a similar time period (11, 12). Therefore, it is unlikely that an increase in penile cancer incidence can solely be explained by a low circumcision rate. Rather, it may be the HPV associated penile carcinogenesis that plays a larger factor in disease incidence in this cohort.

As a driving factor for penile carcinogenesis, the prevalence of HPV induced penile cancer has been shown to be approximately 50% of penile malignancies worldwide (13). Circumcision has also been known to play a role in the prevention of sexually transmitted diseases such as HPV. In addition, the association between circumcision and reduced risk of penile HPV has been well documented in several randomized clinical trials and meta-analyses (14-16). However, it's important to note that these data represent an exclusively adult cohort as there are no studies on the association between infant circumcision and risk for sexually transmitted disease. What can be justified based on this data is the counseling of the benefits of circumcision to an adult male to help reduce his risk of HPV related infection and disease, in addition to modifiable behaviors such as condom use.

Prevention of HPV infection and subsequent penile cancer risk can also be accomplished with vaccines. There are two prophylactic HPV vaccines have been developed that can play an important role in the prevention of HPV transmission. This includes the quadrivalent and 9-valent HPV vaccines (Gardasil and Gardasil 9) that have been licensed for use in females and males (17). The efficacy of these vaccines has been demonstrated in recent studies among HPV-negative men and women (18, 19). Vaccine administration is approved for males aged 9 through 26 years (17) and can be given prior to the counseling of undergoing circumcision later in life. Therefore, it may be reasonable to delay circumcision as a neonate until the patient approaches sexual maturity. This can prevent the need for routine circumcision for all male neonates and reserve circumcision to only those who develop risk factors such as high risk sexual practices or abnormalities such as phimosis or balanitis.

Penile carcinoma can be preventable through advocating daily hygiene and HPV prevention. Although circumcision can help reduce risk factors for penile cancer development, this does not necessarily warrant a requirement for circumcision as a neonate given the rarity of disease and alternative strategies in prevention. Through improved efforts in modifiable behaviors and implementation of HPV vaccination, this can curb penile cancer risk until the patient can make an informed decision regarding circumcision later in life.

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REVIEW ARTICLE

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Forming a stone in pelviureteric junction obstruction: cause or effect?

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ABSTRACT

Objectives: To investigate a possible causal relationship for stone formation in pelviureteric junction obstruction and to outline management options.
Materials and Methods: A literature search and evidence synthesis was conducted via electronic databases in the English language using the key words pelviureteric junction obstruction; urolithiasis; hyperoxaluria; laparoscopic pyeloplasty; flexible nephroscopy; percutaneous nephrolithotomy, alone or in combination. Relevant articles were analysed to extract conclusions.
Results: Concomitant pelviureteric junction obstruction (PUJO) and renal lithiasis has been reported only scarcely in the literature. Although PUJO has been extensively studied throughout the years, the presence of calculi in such a patient has not received equal attention and there is still doubt surrounding the pathophysiology and global management.
Conclusions: Metabolic risk factors appear to play an important role, enough to justify metabolic evaluation in these patients. Urinary stasis and infection are well known factors predisposing to lithiasis and contribute to some extent. The choice for treatment is not always straightforward. Management should be tailored according to degree of obstruction, renal function, patient symptoms and stone size. Simultaneous treatment is feasible with the aid of minimally invasive operative techniques and laparoscopy in particular.

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INTRODUCTION

Pelviureteric junction obstruction (PUJO) is well described in the literature as far as diagnosis and treatment are concerned. Yet, there is much controversy regarding stone formation and management in these patients. PUJO was first described as a syndrome by Dietl in 1864 (1) and the ensuing fibrotic changes were demonstrated by Allen TD in 1970 (2). Subsequently, it was proven that if left untreated the narrow junction eventually leads to deterioration of renal function in the majority of cases (3, 4). PUJO is classified as primary (congenital or intrinsic) when dysfunctional smooth muscle and excess collagen deposition leads to hydronephrosis with clockwise rotation of the renal pelvis and a high ureteral origin (4-7). It also occurs commonly as a secondary (acquired or extrinsic) abnormality, where a crossing vessel (i.e. lower pole artery), a fibrous band or other disease (retroperitoneal fibrosis, renal cysts, xanthogranulomatous pyelonephritis, malignancy)

lead to obstruction by compression and kinking at the junction (8, 9). Concomitant lithiasis of the urinary tract is not uncommon and whether it co-exists as a separate entity or is the result of a narrow renal outflow tract is still debated. The prevalence of lithiasis in patients with malformations of the kidney is described as higher than that of the general population (10). In a retrospective review of 1639 paediatric patients during a 45 year period at the Mayo Clinic, the prevalence was 70-fold that of the aged matched population (11, 12). This seems to be also true for the adult population (13). In an early series, David and Lavengood (14) reported concomitant lithiasis in 16% of patients undergoing open pyeloplasty, whereas others reported an incidence of up to 20% (15). PUJO in horseshoe kidneys is described as high as 35% (16) and Lampel et al. suggested that at least 14% of stones treated in such patients were associated with a narrow pelviureteric junction (17).

We have conducted a literature search in three-3-electronic databases (Medscape/E-medicine, Pub Med, EmBase) using the following key words: pelviureteric junction obstruction; urolithiasis; hyperoxaluria; laparoscopic pyeloplasty; flexible nephroscopy; percutaneous nephrolithotomy, alone or in combination. We isolated articles in the English language, relevant to research and/or reports of concomitant lithiasis on a background of PUJO. Overall, 17 articles were identified, mostly case series and presentation of surgical techniques. Only two reports (11, 13) focused on identifying any underlying pathophysiological changes in paediatric populations, while one further study examined the metabolic factors in renal stones coinciding with PUJO (18).

Pathogenesis of calculi in PUJO

There are few reports in the literature that examine the significance and/or correlation of the ultrastructural changes in the narrow pelviureteric junction with the incidence of renal calcul (11-13). In one such retrospective analysis, all patients had histologic evidence of tissue changes (increased fibrosis) associated with anatomical obstruction, similar to those originally described by Allen TD for true congenital PUJO (13). In theory, an impacted stone at the pelviueteric junction is likely to produce local inflammation and edema sufficient to create circumstances similar to PUJO or it may provoke an inflammatory reaction severe enough to produce a stricture, but strong evidence are sparse (9, 19). It is quite difficult to differentiate between the two at the time of endourological stone treatment and a wise approach is to defer further intervention until more imaging and investigations become available. Another hypothesis is that a delayed washout due to the junction results in crystal agglomeration and nucleation that eventually develop into calculi (20). Whether stones in patients with PUJO have an underlying metabolic causative factor (14, 15) or represent the result of the anatomical condition per se (20) remains an area of controversy. It has been shown that urinary stasis does not appear to be the sole contributor to lithiasis in horseshoe kidneys, and that urinary tract infection and metabolic factors play an important and synergistic role (10). Further evidence from retrospective and prospective studies suggest that urinary stasis may, in fact, have little to do with the pathogenesis of renal stones in PUJO. In their retrospective study, Husmann et al. reviewed medical records of 111 patients who underwent pyeloplasty and simultaneous stone removal with a median follow-up of 10 years. Interestingly, a significant percentage of the study group (n=34, 31%) presented with infectious struvite stones (magnesium-ammonium-sulphate), prompting the authors to sub classify outcomes into struvite and non-struvite groups. In total, 36 patients (32.5%) presented with increased concentrations of several known lithogenic substances in preoperative meatbolic evaluation. The incidence of this finding in these patients was similar to that found in idiopathic stone formers. The abnormality consisted of varying levels of hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia (Table-1). In this cohort, all patients with primary hyperparathyroidism had hypercalciuria and all patients with distal renal tubular acidois had hypercalciuria and hypocitraturia. Long term follow-up of the nonstruvite group (n=53) treated by observation alone yielded a 55% stone recurrence rate, with a median interval to recurrence of 9.5 years. Subsequent metabolic evaluation in this group revealed that 83% had an underlying ab-

Table 1 - Metabolic risk factors for stone formation in patients with PUJO (percentages correspond to those that were metabolically evaluated).

Risk factors Study Series	Hyperoxaluria	Hypercalciuria	Hyperuricosuria	Hypocitraturia
Hussman et al. (13)	N/A	61%(observation group) and 17%(struvite group)	11% (observation group) and 8%(struvite group)	22%(observation group) and 8% (struvite group)
Hussman et al. (11)	N/A	36% (observation group) and 17% (struvite group)	14% (observation group) and 17%(struvite group)	9% (non-struvite only)
Matin and Streem (18)	24% vs 12% in control	33% vs 12% in control	29% vs 8% in control	19% vs 27% in control

normality. In contrast, subsequent medical management in the treatment arm (n=24) yielded only 17% stone recurrence rate. In the struvite group, 43% of recurrent calculi occurred in the contralateral kidney. Long term antibiotic treatment appeared to be beneficial with regards to stone recurrence in this group. The same authors subsequently reviewed a paediatric population with similar characteristics in retrospect, and found a recurrence rate of 68% in long term follow-up, with comparable results as for the metabolic factors found in adults, further supporting the concept of an underlying metabolic etiology (11).

In their prospective observational study, Matin and Streem evaluated 47 patients with congenital PUJO for factors predisposing to lithiasis (18). Of the 21 patients with stones, 67% presented identifiable metabolic risk factors vs. 38% of the 26 control patients with PUJO and no stones. The incidence was not unlike that found in stone forming populations (18, 20). The composition of such stones was found to be calcium oxalate in 93% of patients, with or without calcium phosphate as an additional mineral. The authors acknowledge small number of patients in the study (n=47), but pertain to the prospective design of the evaluation, to conclude that metabolic evaluation is required in the treatment plan of concurrent PUJO and renal calculi. The same conclusion is also produced by Hussman (Table-1) (13). Hyperoxaluria and hypercalciuria have been confirmed as having positive correlation with PUJO and lithiasis in respective series of paediatric patients (21, 22). Summary of the metabolic risk factors identified during these studies is presented in Table-1. In the retrospective study by Bernado et al., 90 patients with PUJO who underwent endopyelotomy and simultaneous stone removal were compared with 80 patients without obstruction who underwent only stone extraction. The authors argue against metabolic factors as a prerequisite, since 71.4% of patients without PUJO were found to have a metabolic abnormality that predisposed to urinary stones, as opposed to 19% with obstruction (23). The authors concluded that correction of the anatomic obstruction facilitates the drainage of urine, thus decreasing the incidence of recurrent urinary stone formation.

Overall, the available evidence point toward a combination of factors that seem to be responsible for lithiasis in PUJO other than urinary stasis caused by the obstruction. An undiagnosed metabolic abnormality and probably genetic predisposition are likely, while urinary tract infection and pH appear to play a part as well. It is therefore important to consider these possibilities and include respective appropriate measures in the formulation of a global treatment strategy.

Management options

In order to adequately manage patients with PUJO and renal stones, one is guided by

answering two important questions, that of when and how to treat. The significance of the exact location and number of the calculi in the pelvicalyceal system is not adequately described in the majority of the studies. An initial period of observation seems reasonable for asymptomatic stones of less than 5mm in greatest dimension, accompanied by regular follow-up of the degree of obstruction and renal function (24). With increasing symptoms, stone size, deteriorating renal function and/or recurrent infections, active treatment becomes necessary. Minimally invasive procedures should be preferred where available. While open, laparoscopic and lately robotically assisted pyeloplasty constitute established treatment options for PUJO, no such consensus exists for treating the stone. For our proposed algorithm in Figure-1, we suggest that PUJO is an already established diagnosis at the time of choice of treatment, preferable by nuclear renogram studies that demonstrate obstruction as part of the pre-operative assessment. In the modern era of endoscopic stone surgery simultaneous treatment appears feasible, even in cases with multiple stones and difficult anatomy, i.e. calyceal stones, where retrograde flexible instruments seem to be very useful (25-28). Table-2 provides a summary of the existing evidence in endoscopic management of such cases. A recently published review by Skolarikos et al. and also laparoscopic series support this concept (29-34). Endoscopic combined intrarenal surgery (ECIRS) could also be an option, although the evidence is lacking. For staghorn and struvite stones in particular, it is prudent to take caution and ensure peri--and postoperative antibiotic cover guided by urine culture and local sensitivity patterns (35, 36). The duration and programming of follow-up is yet to be determined, but should include a history of symptoms, routine renal biochemistry and radionuclide imaging, i.e. MAG-3 renogram as a mini-

Figure 1 - Suggested algorithm for the management of established PUJO and concomitant nephrolithiasis.

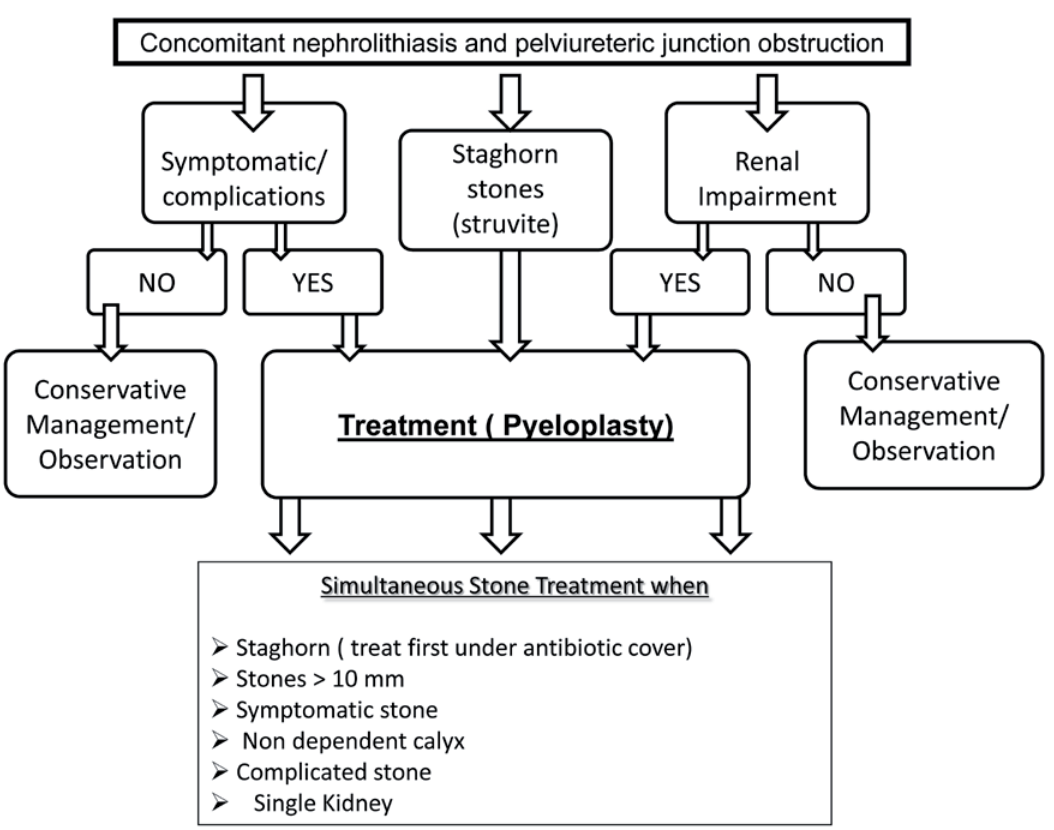

Table 2 - Summary of results following simultaneous PUJO correction and stone treatment.

Study (retrospective series)	PUJO Treatment	Stone Treatment	PUJO reversal	Stone Free Rate (%)	Mean follow-up (months)
Cassis et al. (33)	Antegrade endopyelotomy	PCNL	89%	100%	12
Ramakumar et al. (34)	Laparoscopic pyeloplasty	Flexible cystoscopy/ Pyelolithotomy	90%	80%	12
Ball et al. (27)	Laparoscopic pyeloplasty	Flexible Nephroscope	100%	85%	8.5
Wheelan et al. (28)	Laparoscopic pyeloplasty	Flexible Ureterosocope	90%	100%	13
Agarwal et al. (40)	Laparoscopic pyeloplasty	PCNL	50% (partial)	100%	12
Shrivastava et al. (25)	Laparoscopic pyeloplasty	Flexible cystoscope/ ureteroscope	90%	75%	34
Berkman et al. (26)	Antegrade /Retograde endopyelotomy	Flexible nephroscope/ ureteroscope	71% /90%	N/A	25-29

mum (37, 38). We also recommend performing a thorough metabolic work-up, similar to that proposed for recurrent stone formers, both before and after definitive treatment, in order to identify the metabolic stone formers and formulate an appropriate preventive strategy (39).

CONCLUSIONS

Stone disease in pelviureteric junction obstruction is associated with an underlying metabolic disorder in up to a third of patients. Metabolic risk factors appear to play an important role, enough to justify metabolic evaluation of such patients. Urinary stasis and infection are well known factors predisposing to lithiasis and also appear to be contributory factors. The choice for treatment is not always straightforward and relies on several factors, including organization of the department with dedicated stone clinic services, availability of appropriate equipment to carry out complex endourological surgery and experience in postoperative follow-up and complication management. Upon verification of PUJO with nuclear functional imaging studies, further intervention should be tailored according to degree of obstruction, renal function, patient symptoms and stone burden. Simultaneous treatment is feasible with the aid of minimally invasive operative techniques and laparoscopic approach in particular appears to be the most promising solution (Table-2). Robotically-assisted laparoscopy is rapidly growing in the field and appears promising (40). Metabolic evaluation should be an integral part of initial evaluation as well as follow-up and form the basis for future preventative planning against recurrences.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Female urinary incontinence and sexuality

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ABSTRACT

Urinary incontinence is a common problem among women and it is estimated that between 15 and 55% of them complain of lower urinary symptoms. The most prevalent form of urinary incontinence is associated with stress, followed by mixed urinary incontinence and urge urinary incontinence. It is a symptom with several effects on quality of life of women mainly in their social, familiar and sexual domains. Female reproductive and urinary systems share anatomical structures, which promotes that urinary problems interfere with sexual function in females.

This article is a review of both the concepts of female urinary incontinence and its impact on global and sexual quality of life. Nowadays, it is assumed that urinary incontinence, especially urge urinary incontinence, promotes anxiety and several self-esteem damages in women. The odour and the fear of incontinence during sexual intercourse affect female sexual function and this is related with the unpredictability and the chronicity of incontinence, namely urge urinary incontinence.

Female urinary incontinence management involves conservative (pelvic floor muscle training), surgical and pharmacological treatment. Both conservative and surgical treatments have been studied about its benefit in urinary incontinence and also the impact among female sexual function. Unfortunately, there are sparse articles that evaluate the benefits of female sexual function with drug management of incontinence.

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INTRODUCTION

Urinary incontinence refers to any involuntary leakage of urine with social and hygienic distress, according to the classification of International Continence Society and International Urogynecological Association. It affects men and women, with higher prevalence in women, affecting 15 to 55% (1). In Portugal, according to published data by Portuguese Urological, Neurological and Urogynecological Associations, it is prevalent in 20% of women older than 40 years old, with higher incidence in older women (2). It is an important public health issue due to high prevalence and impact on quality of life (3) and due to financial costs of treatment (4). Clinical investigation of pelvic floor alterations domain generated recommendations and practical guidelines recognized by several international societies of urology and gynecology (5-7). However, they poorly address sexual dysfunctions related to urinary incontinence (although with an evident association, due to anatomic proximity of reproductive and urinary systems) and the impact of sexuality in quality of life and general satisfaction of women (8).

Investigation methodology

A data search was performed at PubMed using the following filters: "sexual function" OR "sexuality" and "urinary incontinence" OR "female incontinence". The articles that included the terms "pelvic organ prolapse" OR "cancer" OR "pregnancy" were excluded. There were 780 articles in total, and it was selected only those that reported clinical trials or review articles (guidelines, meta-analysis, and theoretical or systematic reviews) involving human females not related to pregnancy or post-partum, written in English, French or Portuguese. Two hundred articles were included (49 clinical trials and 151 review articles) related to the objective of the present author. The references of recent published meta-analysis or guidelines prior to publication were excluded, since they exhibited the same evidence level of the compiled article.

Definitions and concepts in Urogynecology

Female urinary incontinence in adults is defined as the involuntary loss of urine, and it is classified in three types: a) stress urinary incontinence (SUI), when it occurs with the increase of abdominal pressure (cough, sneeze, physical exercise, laughing, etc.); b) Urgency urinary incontinence (UUI), concurrent or with immediately following urinary urgency; c) mixed urinary incontinence (MUI), patients with stress and urgency urinary incontinence (not necessarily concurrent) (9, 10). The most prevalent is isolate SUI (51%), followed by MUI (39%) and lastly UUI (around 10%), based on clinical interview and answers of self-applied question forms. In relation to functional urodynamic evaluation, there is an increase of prevalence of pure SUI (51-77%) and reduction of MUI (11-39%), without significant alteration of isolated UUI (10-12%) (11).

SUI

Stress urinary incontinence occurs in the presence of an increase of intra-abdominal pressure without perception of previous micturition desire. It depends on the functional adequacy of urinary sphincter and muscular and ligament structures that support female pelvic floor. When these mechanisms fail and with increase of intra-abdominal pressure (such as laughing, weight lifting, cough, sneezing) it is observed incontinence (12). The risk factors include aging, pregnancy, vaginal delivery and obesity (13). Some others are also considered, but with discrepant research results among authors: hysterectomy, diabetes mellitus, hypoestrogenism associated to menopause (11).

Incontinence grading is hard to perform, and it is admitted that severity is directly related to amount of lost urine (7), although discomfort does not reflect severity. Fultz (2003) evaluated women with urinary incontinence and observed that 28.8% refer moderate to severe discomfort (14). In a practical point of view, some authors suggest that grading may be estimated by the number of pads daily used or by the results of the "pad test" but with some doubts regarding accuracy (6). Conservative treatment of SUI (strengthening and reeducation of pelvic floor muscles) includes physical exercises of pelvic floor muscles-PFMT (pelvic floor muscle training)-and biofeedback and electro-stimulation techniques (15-17). Surgical treatment aims to correct functional inadequacy of urinary sphincter and urethra (injection of submucosal polymers around the sphincter, sub-urethral slings and Burch surgery) (6, 12, 17).

Success rate depends on the used method, but is around 51% to 91% (depending on the analyzing method, definition of cure and follow-up of every patient) (18).

UUI

Urgency urinary incontinence is a symptom of overactive bladder (OBS) with great impact on quality of life (physical, social, psychologic and sexual aspects) (19). OAB syndrome is characterized by pollakiuria and nocturia in the absence of urinary infection or other conditions that cause the symptom. It may be associated with neurological lesions or idiopathic. Many studies on the prevalence of OAB syndrome involve individuals that seek treatment of urinary incontinence, excluding those with urgency without incontinence. In 2014 a meta-analysis was published about the epidemiology of UUI and the authors concluded that prevalence in female patients was 1% to 14%, increasing with age and

directly related to socio-economic status of the population of the studied country (19).

Diagnosis of OAB syndrome is assumed in the presence of urgency urinary symptoms after exclusion of other causative causes. Flow-pressure study may demonstrate hyperactivity of detrusor (not obligatorily), what justifies the symptoms of urgency of the syndrome.

There are no sufficient data for the complete clarification of the physiologic mechanism that generates detrusor hyperactivity, felt as urgency. Except for neurologic lesions (that may provoke involuntary contractions of bladder without superior inhibition), there are four mechanisms accepted that explain detrusor hyperactivity in idiopathic OAB syndrome:

Alteration of reflex mechanism in micturition;

Reduction of innervation of muscular layer of bladder;

Release of acetylcholine in parasympathetic neuronal plaque during bladder feeling with afferent activation of bladder smooth muscle;

Activation of urothelial receptors (mucosal layer that coats bladder) (20).

The objective of OAB syndrome treatment is to eliminate symptoms, although that might be not possible..

Hyperactive bladder syndrome treatment is primarily conservative and includes teaching maneuvers/methods to inhibit involuntary detrusor contractions and strengthening of muscular structures of pelvic floor with directed exercises--PFMT. Pharmacological treatment may also be considered (antimuscarinic and ß3-agonists) for symptoms control. Other lines of treatment include intra-detrusor injection of botulin toxin neuro--stimulation (vaginal electro-stimulation, anterior tibial electro-stimulation or neuromodulation) and exceptionally bladder augmentation enterocystoplasty (5, 6, 16, 17, 20, 21).

Mixed Urinary Incontinence

MUI patients refer incontinence associated with increase of intra-abdominal pressure and also loss or urine prior or simultaneously of urgency without abdominal effort. Patients report differently the proportion of urinary loss according to physical exercise or urgency (22). Diagnosis is based on symptoms and context when they occur. Urodynamic evaluation has little value on diagnosis, since detrusor hyperactivity is identified in only 8% of patients with urgency in the context of MUI (23). It is important to stablish which symptom is the most important (22).

The pathologic mechanisms that generate symptoms of SUI and UUI in the same patient are unknown (23).

MUI treatment aims to treat the main symptoms and the first line of treatment is the conservative recommended PFMT (6). Although there are no randomized studies of the treatment of this pathology, guidelines suggest the treatment of the main component, with a success rate lower than those observed in the treatment of isolated SUI and UUI (22).

Alteration of quality of life (QoL) in patients with urinary incontinence

Most papers of the 80's and 90's discuss conservative and surgical techniques for urinary incontinence and success is defined by objective evaluation of incontinence following each intervention. In the last 10-15 years researches decided to evaluate the impact of urinary incontinence on women's quality of life and success was related to subjective perception of each woman following intervention. In the present, it is recommended to use validated self-applied questionnaires along with physical and auxiliary exams to evaluate several domains of quality of life of women (6, 24). Urinary incontinence is not a life-threating disease, but has a highly negative impact on women's health, affecting several aspects of daily life and quality of life, including personal, work and leisure activities (25).

In 2015, Paul Abrams published an article that evaluated the interference of urinary incontinence in quality of life of female population using an electronic question form applied to 1.203 women with urinary incontinence, with 45 to 60 years old living in USA, France, Germany and United Kingdom. He verified that incontinence grade (number of losses daily) correlated positively with interference in daily life (on daily tasks, social activities and perception of mental health

well-being). The authors stressed the relationship of incontinence severity with impairment of social life, ability to visit friends and impact in familiar life (26). This work is different of previous since it addressed a younger population with intense work, familiar and social life. The results indicated that incontinence is associated with a profound sense of humiliation and stigma (25, 27-29).

The impact on quality of life is transversal to several age groups (30) and the main conditional factors are severity and type of incontinence. All incontinence types are associated to low self-esteem, and higher probability of psychiatric disease (25). The studies show higher levels of anxiety and psychological stress in women with UUI than with SUI, due to unpredictability of detrusor contractions in UUI. Asoglu (2014) verified that women with MUI or UUI had more probability to present anxiety and worse quality of life indexes than those with isolated SUI (1). Same results were obtained by a Portuguese population study by Claudia Senra (31).

The search for care due to incontinence reflects the interference on quality of life and there is a relationship of search for treatment, severity of incontinence and patient's age (32, 33). It is speculated that the reduced search of treatment and high prevalence of incontinence may be related to shame associated (27, 34, 35). Siddiqui (2014) evaluated perceptions of incontinence and their relation to cultural and demographic aspects and concluded that urinary incontinence intimacy is similar among women of different socio-cultural status, developing adaptation strategies such as preventive micturition, identification of bathrooms in public spaces, selection of adequate outfit to eventual loss of urine and restriction of activities that are knowingly associated with incontinence. Globally they verified that women and also health professionals did not value symptoms when they were light. In relation to incontinence experience, the authors evaluated fear, stigma and shame associated, and verified a transversal negative appreciation of urinary incontinence and higher sensation of guilt in non-white population. Religious aspects (Muslims) and cultural aspects (Hispanics) showed a more negative vision of the disease than among other women (27).

Quality of life (QoL) and the treatment of urinary incontinence patients

Globally, the treatment of urinary incontinence involves: 1) PFMT, 2) surgery and 3) pharmaceutic treatment. First line treatment usually is conservative, using exercises for the pelvic floor muscles (PFMT). This recommendation is based on an important meta-analysis using Cochrane Database in 2014 that identified its benefit in all kinds of female urinary incontinence (36). In the same year it was published a prospective article that confirmed the benefits of PFMT in quality of life of patients with urinary incontinence (37).

Surgical treatment of urinary incontinence is mainly directed to women with stress urinary incontinence or with predominance of stress leakage symptoms in mixed incontinence patients. In these cases, it is observed an improvement of quality of life based on the results of self-administered questionnaires regarding urinary symptoms and correlated disturbance of sexual life, that may not suffer the same positive impact (38).

Regarding pharmacologic treatment of urinary incontinence, the studies are mainly directed to patients with urgency incontinence. This a diagnosis based on symptoms and repercussion on quality of life and it is fundamental to determine therapeutic benefits following treatment, using drugs only in patients without cognitive disturbances (5, 6). In spite of the fact that UUI is included in overactive bladder syndrome, the use of drugs is primarily directed to reduce loss of urine episodes (5).

Female sexual dysfunction in female urinary incontinence

The study of female sexuality is very different from the study of male sexuality. Scientific investigation regarding women doesn't receive the same attention than that of male sexual function. Some functional studies destined to men are adapted to women and it is observed an under-valorization of sexual component in relation to reproductive female function. There is a huge gap between knowledge regarding reproductive female function and of female sexual function and its disturbances (39).

Female sexual response

Master and Johnson at the 60's and 70's concluded that sexual response occurrs in a linear and sequential fashion involving four phases: arousal, plateau, orgasm and resolution. In the end of the 70's Helen Kaplan proposed a modification of the sexual response model, reinforcing the role of sexual desire and grouping it in three phases: desire, arousal and orgasm (40). The use of this model of linear sexual response was successively questioned in relation to its applicability in women: many do not present this sexual response, and are considered inadequate, even if they do not considered themselves as such. The sequence of phases was also questioned, since there was an overvaluation of biological and physical phenomena in detriment of conditionings of female sexual pleasure and satisfaction (41). Basson (2001) presented a non-linear model of female sexual response integrating emotional, psychological, and cognitive aspects and external sexual stimulants. According to this model, sexual response starts with sexual desire (spontaneous or not, externally or through cognitive motivation). Sexual arousal includes subjective sensation of arousal or physiological arousal with poor correlation between them (40). The presence of sexual desire and sexual arousal are not sequential although both are important to achieve sexual satisfaction (41). This model is adopted by International Consensus on Sexual Medicine, International Classification of Diseases (ICD-10) and also by the diagnostic and statistical manual of mental diseases (DSM-5) (40).

Female sexual dysfunction and evaluation methods

Prevalence studies on female sexual dysfunction estimate the existence of sexual disturbances in 39-45% of sexually active women (40, 42, 43). This evaluation must be balanced since the studies did not match diagnostic criteria with the data in which the studies were realized (for example, DSM) and symptoms grading. International accepted criteria are present only for the diagnosis of dysfunctions and this is considered when are excluded: 1) Mental diseases not related to sexual function; 2) iatrogenic pharmacological treatment or clinical condition that justifies symptoms; 3) severe disturbance of relationship, 4) violence of partner or 5) other stressing factors (44). Sexual disturbances associated to incontinence cannot be classified as sexual dysfunction according do DSM-5 classification, even with personal suffering and prejudice to sexuality.

The presence of urinary symptoms in incontinent women justifies an adequate gynecological exam and evaluation of sexual function (42, 45). It is also recommended the use of self-administered questionnaires with good diagnostic sensitivity (40). European Urological Association guidelines of diagnosis and therapeutics of urinary incontinence recommend the use of the following question forms to evaluate sexual function in the presence of urinary symptoms: FSFI (Female Sexual Function Index), ICIQ-VS (International Consultation on Incontinence Questionnaire-Vaginal Symptoms), PISQ-IR (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-IUGA revised), SQoL-F (Sexual Quality of Life-Female) and SFQ (Sexual Function Questionnaire) (6, 24). All of them have been used in patients with SUI, UUI and MUI (6). FSFI (46) and ICIQ-VS (47) as well as the earlier version of PISQ-IR (PISQ-12 (48) are validated in Portuguese.

Sexuality and urinary incontinence

Although it is assumed that there is a high probability of influence of urinary incontinence on sexual life, the studies present very different results probably due to the great variability of investigation methods (12). Urinary incontinence may trigger problems related to sexual female life, namely: loss of urine during coitus (coitus incontinence), night losses associated to urgency and fear of bedwetting (49-51). Fear of malodorous and urinary incontinence during coitus are associated with alteration of image and self-esteem responsible for low frequency of sexual activity among incontinent women (52). In elderly population, in the presence of a sexual partner, the occurrence of urinary incontinence has a negative impact on sexuality (8).

Urinary incontinence related to coitus has been described in two ways: urinary incontinence associated to penetration and associated to orgasm ("squirting") (53). Incontinence associated to pe-

netration was associated to SUI and is related to probable intrinsic dysfunction of sphincter, and it is more frequent in women with SUI demonstrated by urodynamic evaluation (18). Coitus urinary incontinence associated to orgasm has been related to detrusor overactivity, although data are not fully clarified (54-58).

Several papers studied the relationship of different kinds of urinary incontinence and sexuality. Asoglu (2014) concluded that urgency symptoms, especially in the presence of MUI, were associated to anxiety disturbances, mood disturbances (depression symptoms) and low quality of life of SUI in the context of sexual life (1). Su (2015) evaluated sexual function in the presence of urinary incontinence, using international validated questionnaires (FSFI) and identified differences among different domains on sexual function according to different types of urinary incontinence. UUI related to reduction to lubrication and increase of pain associated to sexual activity. MUI was related to reduction of sexual satisfaction while SUI did not present any impact on sexual relation (59).

Sexuality after urinary incontinence treatment

Conservative treatment of urinary incontinence using PFMT presented an improvement of functional parameters of the domains desire, arousal and orgasm, regardless the type of urinary incontinence (3). This benefit is mainly relevant in patients with an initial evaluation with significant disturbances of sexual function (59). The studies point an improvement of sexual function with the strengthening of pelvic floor muscles in SUI, including patients with coitus incontinence associated to penetration (1, 2, 60-62).

Surgical treatment of urinary incontinence has been studied in the context of SUI treatment. Published revisions of 2012 (52), 2014 (12), and 2015 (63) highlight the difficulty of evaluation of this parameter due to the absence of uniformization of methodology but recognize the global concern of evaluation of sexual life. It is cited an improvement of sexual function in patients with SUI that also presented coitus urinary incontinence. Women without incontinence during coitus prior to intervention did not present improvement of sexual function even in the presence of improvement of global quality of life. In a percentage of patients submitted to surgical correction of SUI using suburethral slings there is prejudice of sexual function, including reduction of libido, dyspareunia or sexual inactivity. It seems that this report is associated to failure of surgical intervention (12).

Surgical treatment of UUI (through sacral neuromodulation) is poorly studied in relation to sexual function and the existent studies involve small samples of patients but in general show improvement of questionnaire evaluation of sexual function (63-65). In 2015, a meta-analysis was published that considered that there is insufficient data to conclude the impact of sacral neuromodulation on female sexuality (66).

First line of treatment of clinical treatment of OAB syndrome and UUI includes anti-muscarinic and beta3-agonists. There are very few studies about the repercussion of those drugs on sexual function. Only studies of oxibutinin and tolterodin have been published on the subject. Oxibutinin lowered coitus incontinence, associated shame/disturbance and improved sexual life, relationship with partner and increase of sexual interest. Tolterodin showed a higher sexual and mental health based on questionnaires SQoL-F and PISQ-IR and improvement of anxiety scales of evaluation (67). There are no published data about the use of mirabegron (beta3-agonist) on female sexual function.

CONCLUSIONS

The presence of urinary incontinence is associated to stigma, fear, embarrassment and shame related to clinical condition, with repercussion on self-esteem and disturbance of personal, social and sexual life.

Urinary incontinence affects negatively female sexual life. Fear of intimacy associated to sex activity is evident in view of the lower frequency of sexual activity and low sexual and global satisfaction indices among incontinent women. The development of adaptation strategies to incontinence may reduce the impact that the loss of urine may have on sexual activity, but these techniques have greater benefit on stress urinary incontinence.

Conservative treatment (PFMT) of urinary

incontinence improves quality of life and sexuality, regardless the type of incontinence. Studies demonstrate an improvement of quality of life and sexual function after surgical treatment of SUI; the improvement is higher if pre-operatively it is demonstrated the repercussion of incontinence on sexuality. After treatment of UUI, it is identified an improvement of quality of life and sexual function in individuals who receive anticholinergics. Sacral neuromodulation has a positive influence on both domains, but for definite conclusion more studies are necessary.

ABBREVIATIONS

OAB = Overactive bladder
PFMT = Pelvic Floor Muscle training
SUI = stress urinary incontinence
UUI = urgency urinary incontinence
MUI = mixed urinary incontinence
QoL = Quality of life
FSFI = Female Sexual Function Index
ICIQ-VS = International Consultation on Incontinence Questionnaire-Vaginal Symptoms
PISQ-IR = Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-IUGA revised
SQoL-F = Sexual Quality of Life-Female
SFQ = Sexual Function Questionnaire

CONFLICT OF INTEREST

None declared.

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Predictive role of Trimprob associated with multiparametric MRI in the diagnosis of prostate cancer

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ABSTRACT

Objectives: To evaluate the predictive value of TRIMprob test to detect prostate cancer (PCa) in patients referred to prostate biopsy (PB).
Material and Methods: Patients with PSA <10ng/mL and rectal exam without findings suggestive of prostate cancer were selected for TRIMprob evaluation.
Exam was performed by a single operator through transperineal approach.
Patients admitted for the study were submitted to TRIMprob and multiparametric magnetic resonance (mpMRI) and posteriorly to PB.
Results: In total, 77 patients were included. TRIMprob showed evidences of PCa in 25 (32.5%) and was negative in 52 patients (67.5%). The rate of detection of prostate cancer at biopsy was higher in patients with positive TRIMprob (16/25; 64.0%) than in patients with negative TRIMprob (11/52; 21.1%; p<0.001). Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of TRIMprob were respectively 61.5%, 82.0%, 64.0%, 80.3% and 74.0%. ROC curve showed the following areas under the curve values for TRIMprob, mpMRI and combination of TRIMprob + mpMRI: 0.706; 0.662 and 0.741 respectively. At combined analysis, when both TRIMprob and mpMRI were negative for prostate cancer, accuracy was 96.3% or only 1 in 27 PB was positive (3.7%).
Conclusions: Trimprob had similar predictive value for PCa in patients submitted to PB as mpMRI. Combined TRIMprob and mpMRI showed higher accuracy than when performed singly.

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INTRODUCTION

Prostate cancer (PCa) is the most common malign tumor and the second cause of death due to tumor in men worldwide (1). North American data estimate that one in every six men will present PCa, while one in every 36 men will die due to that disease. Since it affects mainly men between 50 and 70 years, it is an important health issue (2). Since population older than 60 years old will triple in the World and reach 2 billion people around 2050, it is expected a natural increase of PCa incidence (3).

The impact of population screening of Pca based on rectal exam and PSA has been continuously debated. It is been discussed the real benefit to detect a high number of patients with clinically insignificant disease and the impact on quality of life due to treatment (4). In general, PSA elevation is followed by prostate biopsy (PB). This

procedure has complication risks such as hematuria (22.0%) and hemospermia (50.0%). Fever is relatively rare (3.5%) as well as sepsis with the need of hospitalization (0.5% of all biopsied men) (5).

Although with well-established indication criteria, around 75% of PB do not show malignancy, with high psychological stress of the patients (6).

In order to reduce the number of unnecessary PB and their associated morbidity, some groups suggest the inclusion of multiparametric magnetic resonance of prostate (mpMRI) for clinical decision (7, 8). mpMRI shows high accuracy for clinically significant PCa detection confirmed during radical prostatectomy (7). mpMRI detects more than 90% of clinically significant prostate tumors. However, it is less reliable to detect small tumors (<0.5mL), low grade disease (Gleason score 6) or tumors at the transition zone (8). However, its high cost avoids the use of mpMRI for population screening in our country.

In 1992, Clarbruno Vedruccio, an Italian physicist, patented a maser ("microwave amplification by stimulated emission of radiation"), a device that produces electromagnetic waves to detect anomalies of biologic tissues. The equipment TRIprob ((TRIMprobe; Finmeccania, Rome, Italy) includes a non-linear oscillator in a cylindrical probe, an analyzer of radiofrequency spectrum and a computer software (9). The probe emits electromagnetic radiation with three frequencies: 465, 930 and 1395MHz. The spectrum analyzer, powered by a receiving antenna, measures signal intensity that are visualized in a computer screen, in three different colors: red, green and blue. The interaction of the electromagnetic field emitted by the probe and the cancerous tissue results in a significant reduction of signal intensity in 465MHz (red bar), while the signals at 930 (green) and at 1395 (blue) do not change. The objective of our study was to evaluate the utility of TRIMprob test as possible screening method to identify patients candidate to transrectal prostate biopsy (9, 10).

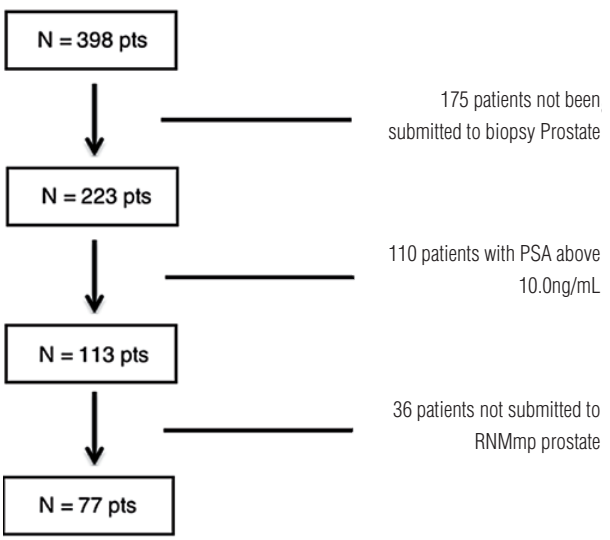
MATERIAL AND METHODS

This is cross-sectional study that included 398 consecutive patients submitted to TRIMprob evaluation from 2012 to 2015 in our institution. All patients with suspicion of prostate cancer and candidate to PB were submitted to TRIMprob. Criteria for PB were determined by the physician and were based on PSA level alteration such as: PSA higher than 2.5ng/mL in patients up to 55 years old and above 4.0ng/mL for patients over 55 years; free PSA/total PSA ratio lower than 20%; velocity of increase of PSA superior to 0.75ng/mL/year and mpMRI of prostate with suspicion of tumor.

The following criteria for inclusion were used to evaluate TRIMprob in patients with suspicion of prostate cancer and to compare the method with prostate mpMRI: 1) patients with PSA lower than 10.0ng/mL and rectal exam without alteration; 2) patients submitted to prostate mpMRI; 3) patients submitted to confirmatory PB and posteriorly submitted to TRIMprob. The exclusion criteria included: 1) patients submitted to previous surgical treatment; 2) patients with history of use of hormonal blockers or 5-alpha-reductase inhibitors. By the end of the study, 77 patients were selected, as illustrated in Figure-1.

In our study, TRIMprob was standardized by transperineal approach by a single operator. The device is composed by a probe, a receptor and a computer screen. The probe measures 30cm in length. Electromagnetic wave penetration (EM) depends on the frequency and dielectrical proprieties of the biological tissues. 465MHz frequency penetrates 20cm (according to calculated dielectrical proprieties of striated muscle and prostate, that are quite similar) and is more adequate for the analysis of perineal region. TRIMprob exam was performed as previously described (10). In summary, patients were dressed with their underwear, standing with the legs a little apart, while the operator positioned behind the patient. According to manufacture's instructions, accepted abnormal values corresponded to less than 40 units during digitalization in 6 standardized and conventional positions. Likewise, aside from the detected resonance values, it was valued a typical pattern of signal reduction at 465MHz below a limit of amplitude that would correspond to the presence or not of prostate cancer. TRIMprob is regularly registered at ANVISA (National Agency of Sanitary Surveillance) under the number 2824 of September, 13th, 2007. mpMRIs

Figure 1 - Study design–175 patients not submitted to prostate biopsy 110 patients with PSA above 10.0ng/mL 36 patients not submitted to prostate mpMRI



were performed in the same device using the classification PI-RADS 1.0 for positivity criteria. Patients with PI-RADS 4 and 5 were considered positive for prostate cancer. PB was performed under local anesthesia (10mL of 1% lidocaine with a needle 22G) guided by transrectal ultrasound. All patients were submitted to biopsy by a needle 16G (11). It was obtained a medium of 17 samples (Table-1). In cases when it was detected suspected lesions at mpMRI at the prostate, the corresponding area was submitted to the collection of three additional samples. Each sample was processed individually and stained by hematoxilin-eosin.

RESULTS

The data of all 77 patients included are shown at Table-2. Mean age was 59.72 years. PSA mean value was 4.79ng/mL (2.26-9.92ng/mL), and the mean prostate volume was 45.31g (17.6-124.0g). By the end of the study, 27 (35.0%) patients were diagnosed with prostate cancer. Final Gleason score 6 (3+3) was the most frequent at PB (40.7%). PCa was associated to higher PSA levels (P=0.021) and alterations at mpMRI (P=0.029) and TRIMprob (p<0.001).

Thirty eight of the 77 patients (49.4%) showed alterations at mpMRI suggestive of prostate cancer. TRIMprob showed alterations suggestive of malign neoplasia in 25 (32.5%) patients. Detection rate of PC at biopsy was significantly higher among patients with positive TRIMprob (16/25; 64.0%) than negative TRIMprob (11/52; 21,1%; P<0,001). At combined analysis, when mpMIR and TRIMprob were negative for PCA, only 1 in 27PB was positive (3.7%) (Table-2). Assuming that the reference standard is the finding of positive biopsies for the diagnosis of prostate cancer, sensitivity, specificity positive predictive value (PPV), negative predictive value (NPV) and accuracy of TRIMprob were 61,5%, 82.0%, 64.0%, 80.3% and 74.0% respectively (Table-3).

We compared the results of TRIMprob with those of mpRI. Also, we analyzed the impact of combination of both exams and their possible predictive value for prostate cancer diagnosis (Table-3). The graphic analysis through ROC curve (Receiving operating characteristics) found the following values of area under the curve for TRIMprob, mpMRI and combination TRIMprob + mpMRI: 0.706; 0.662 and 0.741, respectively. The combination TRIMprob + mpMRI showed the highest index of area under the curve when compared to the single analysis of both methods (Figure-2).

DISCUSSION

Epidemiological data from Brazil show that 37% of all prostate cancer diagnosed correspond

Table 1 - Numerical characteristics of prostate biopsies of 77 patients.

	Variation	Mean	Standard Deviation
Number of collected samples	6-30	17.0	5.225
Number of positive samples	1-10	1.85	3.016

Table 2 - Clinical and pathological characteristics of 77 patients submitted to prostate biopsy.

Variable	Total (%)	Biopsy-	Biopsy+	P value
N	77	50	27	
Age (mean)		59.2	60.7	0.489
40–49 years	6 (7.7)	5 (10.0)	1 (3.7)	
50–59 years	30 (39.0)	19 (38.0)	11 (40.7)	
60–69 years	31 (40.3)	18 (36.0)	13 (48.1)	
>70 years	10 (13.0)	8 (16.0)	2 (7.4)	0.464
PSA (mean)		4.37	5.68	0.021
0–4.0ng/mL	31 (40.3)	23 (46.0)	8 (29.6)	
4.1–10.0ng/mL	46 (59.7)	27 (54.0)	19 (70.4)	0.162
Number of samples (biopsy) (mean)	17.0	17.31	16.65	0.646
Gleason score				
6	-	-	11 (40.7)	
7	-	-	7 (25.9)	
8	-	-	5 (18.5)	
9	-	-	3 (11.1)	
10	-	-	1 (3.7)	
mpMRI				
Negative	39 (50.6)	31 (62.0)	8 (29.6)	
Positive	38 (49.4)	19 (38.0)	19 (70.4)	0.007
TRIMprob				
Negative	52 (67.5)	41 (82.0)	11 (40.7)	
Positive	25 (32.5)	9 (18.0)	16 (59.3)	<0.001
mpMRI + TRIMprob				
Negative	27 (35.1)	26 (52.0)	1 (3.7)	
Positive	50 (64.9)	24 (48.0)	26 (96.3)	<0.001

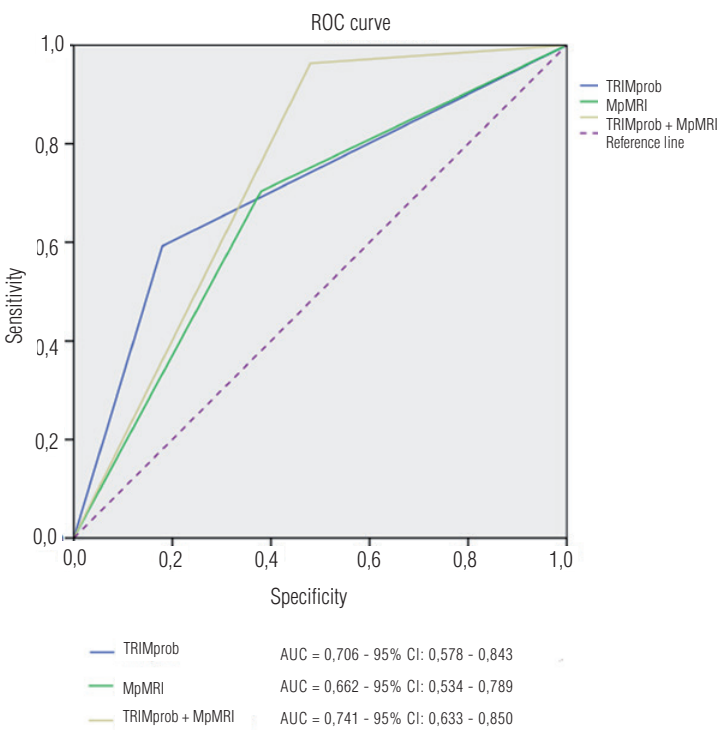
to advanced disease, reinforcing the importance of population screening in our country (12). Unfortunately, PSA specificity in levels >4.0ng/mL is only 60-70% and, therefore, up to 40% of PB are unnecessary (13). Still, false negative rate is also elevated (30-40%), leading to the realization of multiple biopsies with their associated morbidity (14). In that case, the search for other diagnostic methods is justified, in order to identify patients that really need biopsy and to spare those with lower diagnostic risk of PCa.

Several studies show advances of the role of mpMRI to detect PCa (15, 16). A recent meta-analysis by Hamoen et al. showed a combined sensitivity of 88% (CI 95%, 82-93) and a specifici-

Table 3 - Sensitivity, specificity, PPV, NPV and accuracy of TRIMprob and mpMRI and the combination of both in 77 patients submitted to prostate biopsy.

Exam	Sensitivity	Specificity	PPV	NPV	Accuracy
TRIMprob	61.5%	82.0%	64.0%	80.3%	74.0%
mpMRI	70.3%	62.0%	50.0%	79.4%	64.9%
TRIMprob + MRI	96.2%	52.0%	52.0%	96.2%	67.5%

Figure 2 - ROC curves characteristics: results of TRIMprob, mpMRI and combination of both methods in the diagnosis of prostate cancer in 77 patients submitted to prostate biopsy.



ty of 45% (CI 95%, 27-65) in studies using the PI-RADS scale (17). However, mpMRI is very limited to be used in all population due to its cost (18). In that case, TRIMprob has evolved as an alternative for patients candidate to PB. As shown by our study, TRIMprob results were consistent and the method could be used as an additional diagnostic tool to screen patients candidate to PB.

Previous studies confirmed our findings. In 2005, Belloforonte et al. presented their results in 211 patients submitted to TRIMprob and posterior PB. They related sensitivity of 95.4% and specificity of 42.7%. However, the authors included patients with more advanced disease profile, with PSA values up to 38.6ng/mL (19). In our study, we used the PSA level=10ng/mL as superior limit for inclusion, since we believe that most cases with dubious indication of PB have PSA up to this value, in special in patients with no palpable disease. Two other Italian groups also described similar results (20, 21). Gokce et al. showed in 2009 in 148 patients submitted to TRIMprob, sensitivity specificity, PPV and NPV of 76%, 61.3%, 39.6% and 88.5%,

respectively. They suggest the use of TRIMprob for population screening, although with some technical difficulties (22).

Our work is innovative since demonstrated in the same group of men the results of mpMRI and TRIMprob for the detection of PCa. Both methods were useful. Area under the curve of mpMRI was 0.662 while for TRIMprob was higher, 0.706. In 7 patients with PCa, mpMRI was negative and TRIMprob was positive. It was not observed a specific pattern of Gleason score in this group of patients, suggesting that TRIMprob is useful regardless the analyzed group risk. The association of both mpMRI and TRIMprob showed an area under the curve of 0.741. It is important to stress that when both methods were associated, the only case in which PB showed PCa was related to an insignificant clinical disease (single sample with only 20% of prostate adenocarcinoma Gleason 6 (3+3)). These findings reinforce the usefulness of TRIMprob in daily practice, singly or in combination to mpMRI.

Our study has some limitations. It is a retrospective study from a single center and with low number of patients. We defined patients with non-neoplasic disease those with negative biopsies, but it is known that false negative can reach 30% at first PB. However, all patients were submitted to prostate mpMRI and targeted biopsy, increasing the accuracy of PB and reducing the possibility of false negative results. Only with a longer follow-up it will be possible to determine how many of those patients will have prostate cancer in subsequent biopsies.

CONCLUSIONS

Our study showed that TRIMprob was an efficient predictive method for the diagnosis of prostate cancer in patients submitted to PB, with results very similar to mpMRI. When associated, TRIMprob and mpMRI had a higher accuracy than when performed singly. Since it is a more available technical method, we encourage other groups to confirm our results and to reinforce the real impact on screening patients candidate to PB, reducing the number of unnecessary biopsies.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Lack of evidence of HPV etiology of prostate cancer following radical surgery and higher frequency of the Arg/Pro genotype in turkish men with prostate cancer

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ABSTRACT

Objectives: The aim of this study was to assess the possible role of HPV in the development of prostate cancer (PCa) and investigate the distribution of the p53 codon 72 polymorphism in PCa in a Turkish population.
Materials and methods: A total of 96 tissues, which had been obtained using a radical surgery method, formalin-fixed and parafın-embedded, were used in this study. The study group consisted of 60 PCa tissues (open radical prostatectomy) and the control group contained 36 benign prostatic hyperplasia tissues (BPH) (transvesical open prostatectomy). The presence of HPV and the p53 codon 72 polymorphism was investigated in both groups using real-time PCR and pyrosequencing.
Results: The results of the real-time PCR showed no HPV DNA in any of the 36 BPH tissue samples. HPV-DNA was positive in only 1 of the 60 PCa samples (1.7%). The HPV type of this sample was identified as HPV-57. The distribution of the three genotypes, Arg/Arg, Arg/Pro and Pro/Pro was found to be 45.6, 45.6, and 8.8% in the PCa group and 57.1%, 34.3% and 8.6% in the control group, respectively. Compared with the control group, patients with PCa had a higher frequency of the Arg/Pro genotype and Proline allele (odds ratio (OR)=1.67, 95% confidence interval (CI)=0.68-4.09, p=0.044; OR=1.13, 95% CI=0.76-1.68, p=0.021, respectively).
Conclusions: The results of the study do not support the hyphothesis that prostate cancer is associated with HPV infection but indicated that Proline allele can be a risk factor in the development of PCa in the Turkish population.

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Papillomaviridae; Prostatic Neoplasms; Tumor Suppressor Protein p53

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INTRODUCTION

Prostate cancer (PCa) is the most common non cutaneous cancer and the second leading cause of male cancer-related death in the Western countries (1). Risk factors in the development of PCa have been clearly identified as ethnic origin, age, environment and genetic factors (2). In addition, in recent years, it has been reported that sexually transmitted diseases increase the risk of PCa, and genetic and epigenetic changes as well as cell transformation can cause inflammation in the prostate (3, 4).

The prostate can be a target for human papillomavirus (HPV) infections due to its anatomical location (4). Human papillomaviruses (HPVs) are a small and non-enveloped viruses that contain double stranded DNA genomes of approximately 8.000 base-pairs (bp). Of the nearly 200 HPV that have so far been identified, one--third can cause infections in the genital system (5, 6). While low-risk HPV types cause benign lesions, high-risk HPV types such as 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 59, 66, 68, 72 and 81 have carcinogenic potential (6). High-risk HPV types have also been reported particularly in cervical cancer as well as vulvar, vaginal, penile and anal cancers (7). E6 and E7 viral proteins play a significant role in the carcinogenic process where HPV acts as an intermediary. The E6 protein binds to the p53 tumor supressor gene and results in its degradation. The E7 gene bind to the retinoblastoma gene protein of tumor supressors and inactivates it (6).

Many studies have been conducted to explore the association between HPV infection and PCa; however, the possible role of HPV infection in the pathogenesis of PCa remains controversial (8-14). Many researchers have reported that HPV infection has a positive correlation with PCa and increases the risk of PCa (8-10, 13). However, there are also researchers who have suggested that there is no association between HPV infection and the pathogenesis of the PCa (11, 12, 14).

The most commonly mutated p53 tumor suppressor gene is located on chromosome 17p13 and encodes the tumor supressor protein called the "guardian of the genome". This protein has an important role in many cellular process such as cell cycle arrest, DNA repair and apoptosis (15, 16).

The p53 gene has several single-nucleotide polymorphisms. The most common is the codon 72 polymorphism located on the exon 4 (Arg72Pro, rs1042522 G>C). In the 72nd codon of the p53 gene, only one nucleotide alternates the amino acid from Arginine (Arg) (CGC) to Proline (Pro) (CCC). This alternation of the amino acid affects the biochemical and functional characteristics of the p53 protein. The Pro variant strongly activates transcription; however, the Arg variant induces the apoptosis (16, 17).

Despite the abundance of studies on the association between PCa and the p53 codon 72 polymorphism, the results are contradictory (10, 18-22). In some studies, the Arg genotype has been reported to increase the development of PCa (22) while only one study has shown that the Pro genotype reduces the risk of PCa (18).

The aim of the current study was to explore the presence of HPV and the distribution of the p53 codon 72 polymorphism in surgical specimens of localized prostate cancer in a Turkish population using real-time PCR and pyrosequencing methods.

MATERIALS AND METHODS

Sample of the Study

Formalin-fixed paraffin-embedded (FFPE) tissue samples were selected from July 2011 to June 2014 archive collection of the Pathology Laboratory of the Dıskapi Training and Research Hospital, Ankara. To eliminate the possibility of urethral and anal HPV contamination, only samples that had been obtained through radical surgery method were included in the study. The study group consisted of 60 prostate adenocarcinoma tissues (open radical prostatectomy) and the control group was composed of 36 benign prostatic hyperplasia (BPH) tissues (transvesical open prostatectomy). All the study and control cases were of Turkish ethnic origin. None of the patients had received neoadjuvant radiotheraphy or chemotheraphy. The study was approved by the Ethics Committee of Erzincan University.

Tumor Samples

Tissue sections of 3µm wide were stained using hematoxylin eosin and the slides were evaluated by two expert pathologists in terms of the presence of cancer and confirmation of the first histological diagnosis. The histological sections were than manually dissected to determine the area of the tumor for DNA extraction. From each block, 5-10µm sections were obtained for DNA extraction. Samples displaying the characteristics of adenocarcinoma cell infiltration or hyperplasia were selected. These steps were repeated as required until 90% of neoplastic cells were visible.

Tumors were graded according to the Gleason scoring system, and staging was performed according to the 2009 TNM classification (23). Finally, the tumors were assessed using the new grading system for prostate cancer proposed by the International Society of Urological Pathology (ISUP) in 2014 (24). Table-1 presents the demographic and pathologic characteristics of the study samples.

HPV DNA ISOLATION AND DETECTION

DNA Isolation

Tissue sections of 5-10µm thickness were cut from each tissue block and placed in 2mL sterile tubes. For deparaffinization, the samples were incubated in 1mL xylene for 10 seconds, centrifuged at 12.000rpm for 2 minutes and the supernatant was removed. To remove

Table 1 - Clinico-pathological characteristics of the patients.

Variable	Samples	
	PCa (n=60)	BPH (n=36)
Mean age (SD)	63.04±6.67	67.94±8.04
Surgery		
Open Radical Prostatectomy	60 (100%)	0
Transvesical Open Prostatectomy	0	36 (100%)
Gleason Score		
Gleason ≤6	29 (48.3%)	-
Gleason 7	24 (40.0%)	-
Gleason ≥8	7 (11.7%)	-
New Grading System		
Group 1	29 (48.3%)	-
Group 2	14 (23.3%)	-
Group 3	10 (16.7%)	-
Group 4	3 (5.0%)	-
Group 5	4 (6.7%)	-
Pathologic Stage		
T1	0	-
T2	29 (48.3%)	-
T3	30 (50.0%)	-
T4	1 (1.7%)	-
Regional lymph nodes		
Absent	59 (98.3%)	-
Present	1 (1.7%)	-
Distant metastasis		
Absent	0	-
Present	0	-

PCa = prostate cancer; **BPH** = benign prostatic hyperplasia

the remaining xylene, the samples were washed with 1mL absolute ethanol. Following a 2-minute centrifuge at 12.000rpm, the pellets were air-dried for 10 minutes to remove the ethanol. The genomic DNA isolation from the FFPE tissue samples was performed using a QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's recommendations. DNA was eluted in 50µL of buffer ATE and the DNA concentration was measured using the NanoDrop ND-1000 instrument (ThermoScientific, Wilmington, DE, USA), and then stored at-20°C until use.

HPV Genotyping

The presence of HPV in the tissue samples was investigated using mixed primers based on broad-spectrum HPV-DNA amplification and targeting the variable region of HPV L1 ORF. A real-time PCR (EVA GreenTM chemistry) and an HPV sign® Q24 complete kit (Diatech Pharmacogenetics, Italy) able to identify HPV types in a broad spectrum in the Rotor Gene machine were utilized. To control inhibition, the primer set included with the kit for the detection of Human Beta-globin (β-globin) was used. The HPV sign® Q24 complete kit was used according to the manufacturer's recommendations. Each experiment contained at least one negative amplification control (water), HPV sign® positive control and h-DNA control (β-globin control). The presence or absence of HPV DNA was determined using a melting curve analysis. Pyrosequencing was performed on samples that were found to be HPV positive in the melting curve analysis using four specific sequencing primers and the Pyromark Q24 pyrosequencing instrument (Qiagen, Switzerland). Genotype-specific sequencing primers that allowed for the synthesis of 30 base sequences were chosen. These sequences were compared with other sequences in the HPV library and identified using the HPV genotype IdentiFire™ software version 1.0.5.0 (Biotage AB, Uppsala, Sweden).

GENOTYPING OF THE TP53 GENE AT CODON 72

DNA isolation and PCR

The genomic DNA isolation for p53 genotyping was performed as described in the previous section. Four samples were not genotyped due to low DNA quantities. The primers were designed using the pyrosequencing assay design software 2.0 (Qiagen, Hilden, Germany). The PCR amplification of a 155-bp fragment of the p53 gene exon 4 was performed using forward (5'-AGACCCAGGTCCAGATGAAGC) and reverse (5'-biotin CGTAGCTGCCCTGGTAGGTT) primers (Biomers, Germany) with the PyroMark PCR Kit (Qiagen, Hilden, Germany). PCR reactions were performed in a 25µL mix containing 20ng genomic DNA and 5mM of each primer using the following protocol: initial denaturation at 95°C for 15 min., followed by 45 cycles of 95°C for 30 sec, 62°C for 30 sec and 72°C for 30 sec, and a final extension for 10 min. at 72°C.

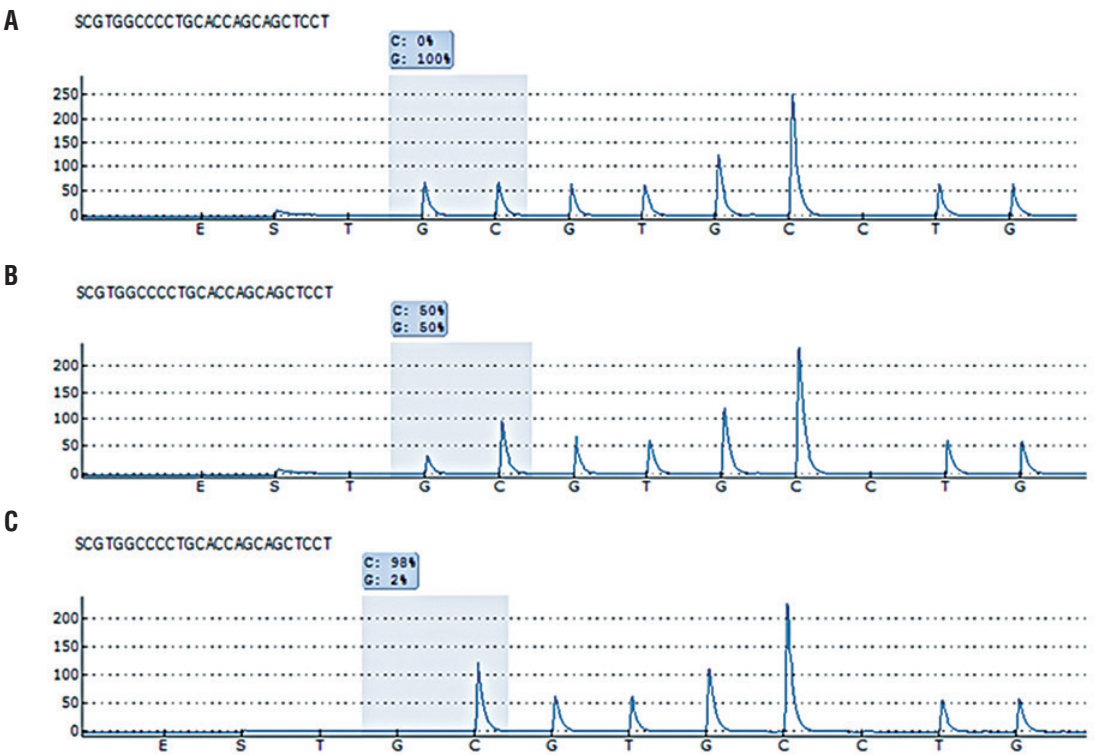
Pyrosequencing

Pyrosequencing reactions were performed using the PyroMark Gold Q24 reagents (Qiagen, Hilden, Germany) and the PyroMark Q24 instrument according to the manufacturer's recommendations. For the pyrosequencing, single-stranded DNA templates were obtained using PyroMark Q24 Vacuum Prep Workstation (Qiagen, Hilden, Germany) according to the manufacturer's recommendations. Briefly, a 10µL PCR product was immobilized in Streptavidin-coated Sepharose High Performance beads (GE Healthcare, Uppsala, Sweden), and processed to obtain single-stranded DNA. The template DNA was incubated at 80°C in a heat block for 2 min. with 25µL of 0.3µmol/L sequencing primer (5'-ATGCCAGAGGCTGCTCCCC) specific for codon 72. To assess the quality of genotyping and raw data, the PyroMark Q24 software (Qiagen, Hilden, Germany) was used (Figure-1).

Statistical analysis

The data was analyzed using the SPSS 17.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). For the analysis of categorical values, the chi-square test ($\chi 2$ test) and Fisher's exact test were used. $p<0.05$ was regarded as statistically significant. The chi-square ($\chi 2$) test was performed to observe the frequency of the genotypes. The expected values of the genotype frequencies were calculated using the Hardy Wein-

Figure 1 - The raw pyrosequencing data for the allelic variants of p53 codon 72 polymorphism (A) arginine homozygote (B) arginine/proline heterozygote (C) proline homozygote.



berg equilibrium (HWE). The odds ratio (OR) and its 95% confidence interval (CI) were determined to measure the correlation between p53 codon 72 Arg/Pro polymorphism in study and control groups.

RESULTS

Presence of HPV DNA in prostate tissues

A total of 96 male patients, 60 with PCa and 36 with BPH, were included in the study. 13.3% of patients with PCa and 44.4% of BPH patients were aged above 70. The mean age of total cohort was 63.04±6.67 years (range 48-75) and 67.94±8.04 years (range 53-89) in the PCa and BPH patients, respectively (p=0.089). Of the PCa patients, 29 (48.3%) were in stage T2, 30 (50%) in T3 and 1 (1.7%) was in T4. Furthermore, the Gleason score was found to be ≤6 in 29 patients (48.3%), 7 in 24 patients (40.0%), and ≥8 in the remaining 7 patients (11.7%). According to ISUP's new grading system, 29 (48.3%) patients with prostate cancer were classified as Group 1, 14 (23.3%) as Group 2, 10 (16.7%) as Group 3, 3 (5.0%) as Group 4, and 4 (6.7%) as Group 5.

The presence of HPV DNA was investigated in 60 (62%) PCa tissues and 36 (38%) BPH tissues. To assess the quality of isolated DNA, the β-globin gene was amplified using the real-time PCR method using the HPV sign® Q24 complete kit. In the Rotor gene Q analysis, all 96 samples (100%) were found to be positive in terms of human β-globin. No HPV DNA was detected using the real-time PCR (EVA Green™ chemistry) with mixed primers targeting a hypervariable region of the HPV L1 ORF in any of the 36 BPH samples. One of the sixty (1.7%) PCa samples was found to be positive for HPV DNA using real-time PCR. Pyrosequencing analysis showed this sample had one type of HPV, namely HPV-57. The HPV-posi-

Table 2 - Genotype and allele frequencies of the p53 codon 72 polymorphism in cancer patients and controls

p53 Arg72Pro	PCa (n=57) n (%)	BPH (n=35) n (%)	p value	OR (%95 CI)
Genotypes				
Arg/Arg	26 (45.6)	20 (57.1)	-	1.0 (reference)
Pro/Pro	5 (8.8)	3 (8.6)	0.337	1.28 (0.27-6.01)
Arg/Pro	26 (45.6)	12 (34.3)	0.044*	1.67 (0.68-4.09)
Alleles				
Arg	31 (72.1)	27 (77.1)	-	1.0 (reference)
Pro	12 (27.9)	8 (22.9)	0.021*	1.13 (0.76-1.68)

p53 Arg72Pro=p53 codon 72 polymorphism; **PCa**=prostate cancer; **BPH**=benign prostatic hyperplasia; **OR**=odds ratio; **CI**=confidence interval; **Arg**=Arginine; **Pro**=Proline;

* p<0.05, considered as statistically significant.

tive sample was classified as pT2cN0M0 and had a low Gleason score (final score 6).

The p53 codon 72 Arg/Pro polymorphism

Due to the low quantity of the isolated DNA, p53 genotyping could not be performed on three PCa samples and one BPH sample. Table-2 presents the genotype frequency in the remaining study and control groups.

The genotypes identified in the p53 codon 72 polymorphism of 57 PCa samples were distributed as follows; Arg/Arg genotype in 26 samples (45.6%), Pro/Pro genotype in 5 (8.8%) and Arg/Pro genotype in 26 (45.6%). Of the 35 BPH samples, 20 (57.1%) had the Arg/Arg genotype, 3 (8.6%) had the Pro/Pro genotype, and 12 (34.3%) had the Arg/Pro genotype.

Comparing the study and control groups based on these results, the Arg/Pro genotype was more frequently seen in patients with PCa than those with BPH and the difference was statistically significant (OR=1.67, 95% CI=0.68-4.09, p=0.044). However, no statistically significant difference was found between PCa and control groups in terms of the frequency of the Arg/Arg and Pro/Pro genotypes (p=0.207; OR=1.28 95% CI=0.27-6.01, p=0.337, respectively).

The frequency of the Arg allele in study and control groups was 72.1% and 77.1%, respectively. Pro allele was observed in 27.9% of PCa patients and 22.9% of BPH cases. In this study, it was also found that the frequency of Pro allele was higher in the PCa patients, thus it can be postulated that Pro allele is associated with PCa (OR=1.13, 95% CI=0.76-1.68, p=0.021).

The p53 codon 72 polymorphism in patients with prostate cancer was investigated comparing the results from Gleason score, ISUP's new grading system and pathologic staging (Table-3). The highest Gleason score was found to be ≤6 for the Arg/Pro and Arg/Arg genotypes while it was 7 for the Pro/Pro genotype. However, there was no statistically significant relationship between the p53 codon 72 polymorphism and the Gleason score (p=0.305). According to the results of the ISUP's new grading system, most of the Arg/Pro and Arg/Arg genotypes were classified as Group 1 while Group 2 was predominant for the Pro/Pro genotype. However, no statistically significant correlation was found between the p53 codon 72 polymorphism and the new grading system (p=0.679). The most frequent pathologic stage was T3 for the Arg/Arg and Pro/Pro genotypes, and T2 for the Arg/Pro genotype. Similar to the results of other

Table 3 - Comparison of the results on the p53 codon 72 polymorphism obtained from Gleason score, ISUP's new grading system and pathologic stage in patients with prostate cancer

			p53 codon 72 polymorphism			Total	p
			Arg/Arg	Pro/Pro	Arg/Pro		
Gleason score	≤6	n	13	1	15	29	0.305
		%	50.0%	20.0%	57.7%	50.9%	
	7	n	9	4	8	21	
		%	34.6%	80.0%	30.8%	36.8%	
	≥8	n	4	0	3	7	
		%	15.4%	0%	11.5%	12.3%	
New grading system	Group 1	n	13	1	15	29	0.679
		%	50.0%	20.0%	57.7%	50.9%	
	Group 2	n	5	3	6	14	
		%	19.2%	60.0%	23.1%	24.6%	
	Group 3	n	4	1	2	7	
		%	15.4%	20.0%	7.7%	12.3%	
	Group 4	n	2	0	1	3	
		%	7.7%	0%	3.8%	5.3%	
	Group 5	n	2	0	2	4	
		%	7.7%	0%	7.7%	7.0%	
Pathologic stage	T2	n	12	1	15	28	0.301
		%	46.2%	20.0%	57.7%	49.1%	
	T3	n	14	4	10	28	
		%	53.8%	80.0%	38.5%	49.1%	
	T4	n	0	0	1	1	
		%	0%	0%	3.8%	1.8%	
Total		n	26	5	26	57	
		%	100.0%	100.0%	100.0%	100.0%	

p53 Arg72Pro=p53 codon 72 polymorphism; **Arg**=Arginine; **Pro**=Proline

methods, the p53 codon 72 polymorphism did not have any significant correlation with pathologic stage (p=0.301).

DISCUSSION

PCa is the most commonly diagnosed cancer in men. However, the etiology and molecular pathobiology of PCa is still not clear. The viral etiology of prostate carcinogenesis, which includes environmental, endogenous and genetic risk factors as well as HPV, is controversial (25).

HPV DNA was first detected in PCa and BPH tissues using PCR in 1990 in a study by McNicol and Dodd; however, the authors did not find a significant difference between the two groups (26). The controversial findings of this study resulted in several other researchers to become interested in this area and carry out further research.

From 1990 to December 2014, there are 40 papers in the literature (excluding case reports and reviews) reporting on the results of tissue-based

studies investigating the association between HPV infection and PCa. Of these, thirty were case-control studies while the remaining 10 only analysed the PCa samples. The prevalence of HPV infection in PCa samples has been reported in range of %0 to 100% (27).

Only 4 of the 40 studies suggested a potential association between the HPV infection and PCa and found a statistically significant difference between the PCa patient group and the control group. One of the early studies was conducted by Anwar et al. (8) who identified 28 different HPV types in 68 PCa samples and reported that all BPH control samples were HPV DNA negative. Sert et al. (9) used a quantitative competitive PCR method to detect HPV 16/E6 and reported a significantly higher number of HPV 16/E6 DNA copies in the PCa samples (10 out of 47 samples, 21%) compared with BPH tissues (1 of 37 samples, 3%).

Leiros et al. (10) reported that 17 (41.5%) of 41 PCa samples (transrectal biopsy samples) were HPV DNA positive whereas none of the BPH samples contained HPV DNA ($p<0.0001$). Martinez-Fierro et al. (13) found the prevalence of HPV DNA to be 20% in PCa samples and 5.3% in the control samples, and suggested a significant relationship between the risk of PCa and the presence of HPV sequences.

Cuzick and Strickler suggested that early studies reported a higher positivity compared with the results of recent studies which found more negativity, and this might be due to HPV contamination with nearby tissues during sampling since HPV DNA was detected in the urethral and anal tissues. Based on this information, some researchers suggested using tissues obtained from radical surgery and microdissection of the neoplastic sample (28, 29).

In the current study, to prevent the HPV contamination of transurethral approach, all samples were obtained using open radical prostatectomy (for the PCa samples) and transvesical open prostatectomy (for the BPH samples). Furthermore, all the tumor samples were reviewed for a second time by two expert pathologists and only the sections that contained tumor cells were included in the analysis of the presence of HPV DNA.

The remaining 36 studies in the literature, however, did not report any difference between the PCa patients and the control cases in terms of the presence of HPV DNA. In the current study, only 1 of 60 PCa samples was found to be HPV DNA positive whereas all 36 BPH samples were HPV negative. Using the pyrosequencing analysis, the type of HPV positive sample was identified as HPV-57, which is considered to be low-risk and associated with skin lesions. A retrospective assessment of the patient with HPV-57 showed that the patient had genital wart. It was considered that the PCa sample was contaminated during the open radical prostatectomy. Despite the difficulty of presenting conclusive evidence for negative results, our DNA samples were of sufficient quality to amplify the human control gene (β-globin), and the internal amplification control showed that the extraction protocol did not inhibit the PCR.

The data obtained in the current study is in agreement with the results of two studies; one by Bergh and the other by Sfanos. Bergh analyzed 352 samples (171 PCa and 181 BPH) and Sfanos investigated 200 PCa samples. Neither detected HPV-DNA in prostate tissue samples (11, 12).

Storey et al. (1998) showed that the p53 homozygotes pose a high risk for the patients in terms of developing HPV-associated cervical cancer (30). Since then, a considerable number of studies have been conducted to explore the association between the p53 codon 72 polymorphism and various cancer types such as breast, pancreas, colorectal, lung and bladder cancer; however, these studies reported contradictory results (17).

In recent years, researchers have suggested that the p53 codon 72 polymorphism has a significant role in the development of tumors and the progression of PCa; however, contradictory results have been reported (18-22). Wu et al. (21) found that the Pro genotype is 2.6 times more frequent than the Arg variant in patients with PCa and the difference was statistically significant. In another study by Henner et al. (18), p53 Pro homozygosity in men reduced the risk of developing PCa and therefore Pro allele can have a protective effect. Doosti and Dekhordi (22) found a significant difference between PCa patients and the control group in terms of the Arg/Arg genotype and the frequency of Arg allele, and suggested that the Arg/Arg genotype can be a risk factor for the development of PCa in Southest Iran.

On the other hand, four studies did not find any association between the p53 codon 72 polymorphism and PCa. Huang et al. (20) suggested that there is no correlation between PCa and the p53 codon 72 polymorphism and put forward the hypothesis that p21 codon 31 polymorphism is associated with both the development of PCa and BPH. Leiros et al. (10) concluded that there is no correlation between p53 codon 72 polymorphism and HPV positive and negative PCa and hyperplasia. Salehi and Hadavi (31) reported no significant difference between the tumor and control groups and concluded that neither the p53 codon 72 polymorphism nor HPV infection results in susceptibility to PCa in an Iranian population.

Michopoulou et al. (2014) who conducted a study with 50 samples obtained from a Greek population, found HPV positivity in 8 PCa samples (16%) and 1 control sample (3.3%) using the real-time PCR method. Furthermore, the authors explored p53 codon 72 polymorphism in the same patients and found the distribution of three genotypes namely Arg/Arg, Arg/Pro, and Pro/Pro to be 69.6, 21.7, and 8.7%, respectively in the PCa group, and 75.0, 17.86, and 7.14%, respectively in the healthy control group. The authors did not report a statistically significant difference between HPV presence and factors such as age, stage, p53 codon 72 polymorphism and PCa (32).

Due to these contradictory results and the lack of reliable data on the genotype distribution of the p53 codon 72 polymorphism in a Turkish population, we conducted the current research with PCa patients and a control group. Comparing the genotype frequency of the two groups, it can be postulated that in the Turkish population, the Arg/Pro genotype and Pro alleles are more frequently seen in patients with prostate cancer.

The apoptosis-stimulating proteins (ASPP) of the p53 family regulate the function of apoptosis of the p53 codon 72Arg / Pro polymorphism. The apoptosis function of the p53 codon 72Pro variant is selectively inhibited by apoptosis-stimulating protein inhibitors (iASPP). The strong capacity of the p53 codon 72Arg variant to induce apoptosis results from its ability to escape from iASPP inhibition and its even greater abilitiy to localize to the mitochondria. Apoptosis is less frequently seen in people with the p53 codon 72Pro/Pro genotype compared with those with the Arg/Arg genotype and therefore Pro allele is more susceptible to the development of cancer (33). This is also supported by the results of the current study.

As in all research studies, this study also has certain limitations. Since the tissue samples had been obtained from patients with localized prostate cancer treated with radical prostatectomy, the number of samples was relatively smaller and thus the statistical power and potential bias of the study were limited. We did not have access to these samples because surgical treatment is not among the treatment options for advanced stage prostate cancer and metastatic cases. Furthermore, prostate biopsy is used in the follow-up of patients with high grade PIN; therefore, the tissues of these patients were not available. In addition to that this was a retrospective study, in which we did not have access to the blood samples of the patients, we could not perform an HPV serology. The last limitation of the study was that the control group consisted of samples with BPH; however, a control group with normal prostate tissue may have been more appropriate to show the association between prostate carcinogenesis and HPV infection.

CONCLUSIONS

This is the first study that investigated the etiological role of HPV and the p53 codon 72 polymorphism in the development of PCa in a Turkish population. The results of the present study do not support the hyphothesis that prostate cancer is associated with HPV infection but indicate that Proline allele can be a risk factor for the development of PCa in the Turkish population. Further studies with larger series are needed to investigate the potential role of HPV in prostate carcinogenesis.

ABBREVIATIONS

HPV = human papillomavirus
PCa = prostate cancer
BPH = benign prostatic hyperplasia
BP = base-pairs
Arg = arginine
Pro = proline

FFPE = formalin-fixed paraffin-embedded
β-globin = beta-globin
SPSS = Statistical Package for Social Sciences
HWE = Hardy Weinberg equilibrium
OR = odds ratio
CI = confidence interval
ASPP = apoptosis-stimulating proteins
iASPP = apoptosis-stimulating protein inhibitors

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT: LACK OF EVIDENCE OF HPV ETIOLOGY OF PROSTATE CANCER FOLLOWING RADICAL SURGERY AND HIGHER FREQUENCY OF THE ARG/PRO GENOTYPE IN TURKISH MEN WITH PROSTATE CANCER

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The authors retrospectıvely evaluated the presence of HPV and the p53 polymorphism distribution by RT-PCR in a series of 60 surgical specimens of localized prostate cancer and 36 BPH samples. They found HPV in only one prostate cancer case and no HPV in BPH cases. They also demonstrated that Ar72Pro polymorphism and the Proline allele were more frequently found in cancer. They concluded that there is no association between prostate cancer and HPV and also postulate that the Proline allele can be a risk factor for the development of PCa in the Turkish population.

The article's subject is not original, the author (1) themselves recognized that there is a plenty of data about the association of HPV infection and prostate cancer risk in literature. The novelty relies in the correlation between the p53 polymorphisms and the prostate cancer prognostic factors Gleason score, pathologic stage, and ISUP grading. The small sample size is a serious limitation of this paper, specialy to infer about genotype frequences in a specific population, which the authors have already recognized at discussion section. While not original and statisticaly underpowered I think that article brought some data that expanded our knowledge of prostate carcinogenesis.

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ORIGINAL ARTICLE

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Predictive value of [-2]propsa (p2psa) and its derivatives for the prostate cancer detection in the 2.0 to 10.0ng/mL PSA range

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ABSTRACT

Introduction: To assess predictive value of new tumor markers, precursor of prostate specific antigen (p2PSA) and its derivates-%p2PSA and prostate health index (PHI) in detection of patients with indolent and aggressive prostate cancer (PC) in a subcohort of man whose total PSA ranged from 2 to 10ng/mL.

Materials and Methods: This cross-sectional study included 129 consecutive male patients aged over 50 years, with no previous history of PC and with normal digital rectal examination findings, but with serum PSA in interval between 2 and 10ng/mL. All patients underwent standard transrectal ultrasonography guided prostate biopsy for the first time. For all patients, serum PSA, free PSA (fPSA) and p2PSA were measured and PHI and %p2PSA were calculated.

Results: PHI and %p2PSA levels were significanlty higher in patients with PC compared to those without this malignancy. The same findings have been observed in group of patients with Gleason score ≥7 compared to those with Gleason score <7. ROC analysis reveled the highest area under the curve with these two markers. Multivariate logistic regression showed significant improvement in PC detection and its agressive form (assumed as Gleason score ≥7).

Conclusions: New markers, derivates of p2PSA (especially %p2PSA and PHI), represente potentially very important clinical tool for predicting presence of PC, and even more important, to discriminate patients with Gleason score <7 from those with Gleason score ≥7 with total PSA in range from 2 to 10ng/mL.

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INTRODUCTION

Prostate cancer (PC) is the fifth leading cause of cancer in male population worldwide. In western countries, it represents the most commonly diagnosed cancer in men. Autopsy studies highlighted the fact that the prevalence of PC in men 70 years of age or older is around 80% (1-3).

Prostate-specific antigen (PSA) is widely known as a main serum biomarker for the early detection of PC (4). Namely, its introduction in routine urological clinical practice in the early 1980s deeply influenced PC diagnosis and management, with a consequent reduction in PC-related mortality during the past three decades (5-7).

However, keeping in mind the fact that PSA is an organ-specific but not cancer-specific marker, numerous limitations could appear during evaluation of this screening test validity. Firstly, it has been recognized that PSA has a low speci-

ficity, with the positive predictive value around 25%, leading to a huge number of false-positive results and up to 75% unnecessary prostate biopsies. Secondly, PSA also has low sensitivity, with about one-third of all PC cases with the level of this marker below the value of 4ng/mL. Finally, the findings from numerous studies have been highlighted that almost 60% of all PC operative treated patients had so-called indolent tumors, characterized with low malignant potential (8, 9). Keeping in mind this fact, it could be hypothesized that majority of these patients were over-detected and subsequently over-treated. All these facts clearly pointed out that PSA alone has no satisfied predictive value in PC detection.

Consequently, in more recent years, considerable efforts have been made to find new specific markers for early PC detection with improved potential to detect its aggressive clinical form. In this line, the introduction of several PSA derivatives (free PSA [fPSA], percentage of free PSA [%fPSA], PSA density, PSA velocity, Prostate health index [PHI],) in clinical practice significantly improved the accuracy and validity of PSA in identifying PC. Moreover, fPSA was found to include several subforms, such as a precursor form of PSA (proPSA). Theoretically, seven isoforms of proPSA should exist of which [-2] proPSA (p2PSA) is the most stable form. The results from several studies suggested that p2PSA has the highest specificity in PC detection (10, 11). It originates mainly from malignant prostate epithelium, especially in periphery zone of prostate, which is the dominant location of cancer occurrence (12, 13). Therefore, nowadays this marker represents the most promising tool for early PC detection. Additionally, it has been shown that p2PSA is also capable to make distinguish between clinically insignificant tumor (low grade) and cancer that needs to be treated.

Keeping in mind all mentioned above, the objective of this study was to *assess predictive value of* tumor markers p2PSA and its derivates, %p2PSA, and PHI in detection of patients with aggressive PC (assumed as Gleason score ≥7) in a sub-cohort of men whose total PSA ranged from 2 to 10ng/mL.

MATERIALS AND METHODS

Design, setting and participants

Study was conducted in Clinic of Urology, Clinical Center of Serbia, Belgrade, from January 2012 to January 2014. This cross-sectional investigation included 129 consecutive patients who underwent prostate biopsy for the first time. Inclusion criteria were: age over 50 years, no previous history of PC, normal digital rectal examination findings, serum PSA in interval between 2 and 10ng/mL, and minimally 12 biopsy cores taken from patient. Exclusion criteria were: previous consumption of medications that influence on PSA level (Finasteride, Dutasteride), previous surgical intervention on prostate (Transurethral prostatectomy TURP, biopsy), acute prostatitis, urinary tract infection, and previous androgen therapy.

Study was approved by Ethic Committee of Clinical Center of Serbia and Faculty of Medicine, University of Belgrade. All patients were completely informed about procedure and possible complications. Written consent was obtained from all patients.

Interventions, measurement and data collection

At first examination, complete patient history (urological and general) and urological examination was done. Subsequently, blood samples were drawn and immediately stored in refrigerator at 4°C temperature. Serum samples from whole blood were obtained by centrifuge and stored at-20°C. When all samples were collected, serum PSA, fPSA and p2PSA were measured. Our laboratory routinely measures only serum PSA levels by Abbott test with CMIA technique. Access Hybritech assays (Backman Coulter Inc., Brea, CA, USA) were used to measure serum PSA, fPSA and p2PSA. p2PSA is measured using Hybertech p2PSA automated immunoassay. Hybritech calibrations were used for PSA and fPSA levels. After obtaining p2PSA, fPSA and PSA results, these were combined to calculate PHI:

PHI = (p2PSA/fPSA) x (square root of PSA) (equation 1)

In addition, %p2PSA was calculated using following formula:

%p2PS = p2PSA / (fPSAx1000) x 100. (equation 2)

Blood analysis also included C-reactive protein (CRP), serum protein and testosterone.

Physical examination comprised digital rectal examination. Furthermore, all participants underwent standard transrectal ultrasonography guided prostate biopsy. Minimal 12 cores biopsies were taken. Six cores were taken from peripheral zone of each lobe, 2 of those cores were form apex, 2 from middle part and 2 from base of prostate.

Preparation of biopsy core and microscopically examination was done in Department of Pathology, Clinical Center of Serbia. Biopsy specimens were placed in specific single-core specimen containers and then processed and evaluated by experienced genitourinary pathologist. Prostate cancer was identified and graded according to International Society of Urological Pathology definitions (14).

Pathological findings were divided into two groups, with and without PC. Findings of patients with confirmed cancer were further investigated to calculate Gleason score. Afterward, patients with cancer were divided into subgroups depending on Gleason score, patients with score less than 7 and patients with 7 and higher Gleason score.

Statistical analysis

Data are presented as counts (percents), mean±sd or median (25th-75th percentile), depending on data type and distribution. T test and Mann-Whitney U test tests were used for group comparisons. Receiver operating characteristics (ROC) area under the curve (AUC) was used to assess significant marker of PC and to determine cut-off value. Univariate and multivariate logistic regression were used to fit prediction of PC by explanatory variables. Hosmer-Lemeshow test was used to check for goodness of fit of logistic regression model (calibration of the model). All statistical analyses were performed in SPSS 20.0 (IBM corp.) statistical software. All p values less than 0.05 were considered significant.

RESULTS

Study included 129 patients, 65 with PC (50.4%) and 64 without PC (49.6%). Basic clinical characteristics of the study population are presented in Table-1. Significant differences between examined groups were observed in fPSA, %fPSA, %p2PSA and PHI. There were no significant differences between groups in respect of values of proteins, CRP and testosterone. Furthermore, mean age was also very similar in both groups.

The distribution of the PSA value category according to the presence of PC is shown in Table-2. According to this analysis, there was no statistically significant difference in this variable among patients with and without presence of this malignancy (p=0.820).

Table-3 represents area under the curve (AUC), cut off values and sensitivity and specificity for each chosen cut off value. Left side of the table represents AUC for all patients (PC and controls) while right side of the table represents AUC only for patients with PC. When analyzing diagnosis of PC, the highest area was observed in %p2PSA, following by fPSA and %fPSA, while the lowest observed in tPSA. We presented three cut--off values for %p2PSA and PHI because no adequate cut off was obtained on ROC graph. But, of those three variants, best ratio of sensitivity and specificity for %p2PSA would be at cut-off 1.67 and 41.67 for PHI. When analyzing diagnosis of GS ≥7 only PHI and %p2PSA are significant (PHI is almost significant, very close to conventional level of significance, 0.05). Same as for diagnosis of PC, three possible cut-off values for PHI and %p2PSA are present.

Univariate and multivariate logistic regression were used to assess predictive value of PSA isophorms (Table-4 and Table-5). In whole sample model, univariate analysis revealed that fPSA, %fPSA, PHI and %p2PSA are significant predictors of PC. Also, %p2PSA has highest R^2 which suggests that it is the best marker for PC. In multivariate model, p2PSA, PHI and %p2PSA are significant predictors of PC. In PC group, %p2PSA

Table 1 - Basic characteristics, labaratory and Prostate Specific Antigen.

	PCa	Non-PCa	p value
Age	65.3±6.6	64.0±6.6	0.281
tPSA	5.81±1.98	6.24±1.96	0.220
fPSA	0.84±0.46	1.21±0.62	<0.001
%fPSA	14.67±7.27	19.06±7.52	<0.001
p2PSA	19.55±14.93	18.68±12.46	0.779
%p2PSA	2.39±1.35	1.61±0.62	<0.001
PHI	54.77±31.21	39.15±15.59	<0.001
Protein	77.10±4.74	78.10±4.85	0.252
CRP	1.90 (1-3.8)	1.75 (0.9-3.3)	0.532
Testosterone	19.18±6.93	18.63±6.19	0.795

*Med (25^{th} -75^{th} percentile)

Table 2 - Distribution of patients with or without prostate cancer according to total prostate specific antigen.

Total PSA	Prostate cancer	
	No	Yes
2-2.9	4 (6.2%)	5 (7.7%)
3-3.9	6 (9.4%)	8 (12.3%)
4+	54 (84.4%)	52 (80.0%)

No significant difference between groups (p=0.808)

is significant (PHI and p2PSA are almost significant, very close to conventional level of significance, 0.05).

DISCUSSION

Early detection of PC remains the most important issue for general practitioners, patients, researchers, and the experts in the field of urology. During the past decades, efforts are being made to identify tools or biomarkers that can maximize early diagnosis of aggressive disease, but curable, and minimize the undesirable effects of treatment of indolent disease.

In our study, we examined the relationship between PC (presence and aggressiveness according to the value of Gleason score) and the level of the PSA, and its derivates, especially %p2PSA and PHI. To the best of our knowledge, this kind of investigation is the very first one conducted in Balkan population. According to results of our study, investigated biomarkers could distinguish benign from malign changes in prostate and between high and low malignant potential tumor changes in patients with confirmed PC. The findings in our study indicated that p2PSA, %p2PSA and PHI were independent predictors of this malignancy. Also, they showed promising predictive

Table 3 - Area under the curve AUC.

	Controls vs Prostate cancer (n=129)					Gleason <7 vs ≥ 7 (n=65)				
	Area	p value	Cut off	Sn	Sp	Area	p value	Cut off	Sn	Sp
tPSA	0.563 (0.464-0.662)	0.215	3.47	90.6	9.2	0.538 (0.389-0.687)	0.608	3.530	92.0	10.0
			5.55	62.5	49.2			5.275	64.0	45.0
			8.42	15.6	90.8			8.175	16.0	90
fPSA	0.707 (0.617-0.798)	<0.001	0.550	90.6	29.2	0.520 (0.375-0.664)	0.793	0.400	90.0	16.0
			1.035	60.9	81.5			0.665	67.5	40.0
			1.520	21.9	90.8			1.525	10.0	92.0
%fPSA	0.693 (0.602-0.785)	<0.001	11.410	90.6	40	0.529 (0.386-0.671)	0.701	6.825	90.0	8.0
			12.905	81.3	49.2			11.24	65.0	60.0
			22.565	25.0	90.8			21.95	15.0	92.0
p2PSA	0.514 (0.414-0.615)	0.779	8.205	90.6	13.4	0.581 (0.436-0.726)	0.275	7.770	92.0	15.0
			13.020	60.9	61.5			15.24	64.0	40.0
			32.160	9.4	90.8			28.41	16.0	90
PHI	0.680 (0.588-0.772)	<0.001	27.480	90.6	26.6	0.645 (0.505-0.784)	0.054	31.33	91.7	22.5
			41.670	64.1	62.5			49.13	66.7	60.0
			61.015	28.1	90.6			76.38	25.0	90
%p2PSA	0.723 (0.632-0.810)	<0.001	1.245	90.8	34.4	0.673 (0.534-0.812)	0.020	1.356	92.0	20.0
			1.673	75.4	64.1			2.495	56.0	17.5
			2.368	43.1	90.6			3.076	32.0	90

Table 4 - Univariate model for prostate cancer prediction and ≥ 7 Gleason score.

	Controls vs Prostate cancer (n=129)				Gleason <7 vs ≥ 7 (n=65)			
	P value	OR (95% IP)	R^2	H-L[a]	P value	OR (95% IP)	R^2	H-L[a]
tPSA	0.219	0.894 (0.749-1.069)	0.016	0.925	0.663	1.058 (0.820-1.367)	0.004	0.946
fPSA	0.001	0.247 (0.110-0.553)	0.148	0.025	0.547	0.700 (0.220-2.232)	0.008	0.040
%fPSA	0.002	0.920 (0.872-0.970)	0.111	0.604	0.419	0.970 (0.902-1.044)	0.014	0.506
p2PSA	0.737	1.004 (0.981-1.028)	0.001	0.548	0.116	1.028 (0.993-1.063)	0.061	0.185
PHI	0.001	1.037 (1.015-1.060)	0.146	0.993	0.052	1.021 (1.000-1.042)	0.102	0.983
%p2PSA	<0.001	3.016 (1.715-5.305)	0.207	0.574	0.024	1.880 (1.086-3.256)	0.150	0.869

[a] Hosmer and Lemeshow test p value

Table 5 - Multivariate model for prostate cancer prediction and ≥ 7 Gleason score.

	Controls and Prostate cancer (n=129)				Gleason <7 and ≥ 7 (n=65)			
	P value	OR (95% IP)	R^2	H-L[a]	P value	OR (95% IP)	R^2	H-L[a]
tPSA	0.394	1.175 (0.811-1.702)			0.589	1.137 (0.714-1.809)		
fPSA	0.074	0.152 (0.019-1.198)	0.160	0.247	0.631	0.505 (0.031-8.201)	0.020	0.932
%fPSA	0.851	1.011 (0.901-1.135)			0.928	1.007 (0.857-1.185)		
tPSA	0.385	1.178 (0.814-1.705)			0.583	1.142 (0.711-1.835)		
fPSA	0.006	0.042 (0.004-0.407)	0.266	0.118	0.204	0.131 (0.006-3.013)	0.148	0.949
%fPSA	0.767	1.018 (0.907-1.142)			0.824	1.019 (0.864-1.202)		
p2PSA	0.007	1.086 (1.023-1.152)			0.058	1.059 (0.998-1.125)		
tPSA	0.939	1.015 (0.689-1.495)			0.879	1.039 (0.636-1.696)		
fPSA	0.131	0.208 (0.027-1.598)	0.268	0.358	0.600	0.461 (0.025-8.358)	0.116	0.554
%fPSA	0.744	1.019 (0.908-1.145)			0.828	1.019 (0.863-1.203)		
PHI	0.004	1.037 (1.012-1.064)			0.065	1.021 (0.999-1.044)		
tPSA	0.396	1.179 (0.806-1.725)			0.532	1.165 (0.721-1.882)		
fPSA	0.135	0.211 (0.027-1.623)	0.279	0.044	0.614	0.477 (0.027-8.486)	0.163	0.562
%fPSA	0.760	1.018 (0.906-1.145)			0.808	1.021 (0.864-1.205)		
%p2PSA	0.003	2.451 (1.361-4.414)			0.027	1.848 (1.071-3.189)		

[a] Hosmer and Lemeshow test p value

value for detection of high malignancy potential, especially %p2PSA which achieved the best results and statistical significance. Other two are near statistical significance and it is very likely that larger sample size could provide significance. Also, in multivariate models, it has been shown that inclusion of p2PSA, %p2PSA and PHI increased prediction of PC presence and level of its aggressiveness (assessed by Gleason score), although p2PSA and PHI did not reach conventional level of statistical significance in Gleason score groups (<7 and 7+), but p values are very close to 0.05.

During the past years numerous studies have been performed in other to explore the predictive value of different biomarkers in PC detection (15-22). Le et al. showed evidence in distinguishing PC from benign disease using the %p2PSA in 2.034 men with PSA between 2.5 and 10ng/mL, normal DRE (20). Moreover, in their investigation, Stephan et al. showed that the PHI, the absolute value of 60, had greater power to predict clinically significant prostate cancer (Gleason ≥7) compared to p2PSA, %p2PSA, total PSA and %fPSA (21). Loeb et al. also presented evidence that supports the PHI to distinguish men with clinically significant prostate cancer (Gleason ≥7) compared to the tPSA (22). Therefore, the results from these studies consistently showed that p2PSA and its derivates represented improved and more reliable prognostic tools for PC detection, especially for those cases with Gleason score of 7 and more. It has been widely hypothesized that %p2PSA and PHI could be the best predictors of PC presence, with the significantly better accuracy than commonly used makers such as tPSA and %fPSA (11, 18, 20). The results from Serbian PC

population confirmed and extended these findings and also provided further evidence that %p2PSA and PHI could be considered as power tools for improvement the accuracy in the early detection of clinically significant PC.

In our investigation, we used ROC and AUC analyses, as a part of comprehensive statistical approaches in assessing significant cut-off values of different potential PC biomarkers. Extensive employment of the existing literature led to the conclusion that %p2PSA and PHI have the highest AUC, leading to the hypothesis that these indicators represented the most promising predictors of prostate malignancy (10, 11, 23-26). According to these findings, PHI has the highest AUC, but very similar to %p2PSA. The results from our study have revealed that in our cohort of males %p2PSA represented leading PC biomarker, with the highest AUC. This potential predictive ability has been noted in both, discriminating benign from malignant prostate tumor, and more aggressive (Gleason score ≥7) from less aggressive forms of PC (Gleason score <7). Similar to other authors, PHI revealed high discriminating power, but less than %p2PSA, especially in discriminating high aggressive forms of PC from less aggressive forms. Results of our study also indicated high discrepancy between sensitivity and specificity of these markers. Similar to other researchers, 90% sensitivity is followed by low specificity and vice versa. Nevertheless, %p2PSA and PHI demonstrated the best ratio between sensitivity and specificity. Since ideal combination of sensitivity and specificity in our study is not available, we presented cut off values for combination of sensitivity and specificity of 90%, which is also suggested in others similar investigations (19, 26, 27).

With the aim to assess the independent predictors of prostate malignancy, we also performed the logistic regression analyses. The results from univariate logistic regression showed that %p2PSA and PHI had the highest predictive value for PC detection, as well as for distinguished clinical form with Gleason score ≥7 from the non-clinically significant one. The results from this type of analysis were in accordance with those obtained in ROC analysis. Namely, %p2PSA appeared to be a better indicator of malignancy than PHI, especially when aggressive form is the dependent variable. In this regression analysis PHI is also near conventional level of significance (p value is 0.054 in AUC analysis and 0.052 in logistic regression) and it is possible that higher sample size could reach statistical significance at conventional level. However, in multivariate model, %p2PSA remained significant predictor of PC and its aggressive forms, but PHI remained significant only in PC prediction. It is very important to note that in prediction of aggressive form, p value is higher in multivariate than in univariate model. Therefore, the addition of %p2PSA and PHI in multivariate model improved model itself, and made decision process more accurate, if based on this probability (21). Our results are in accordance with the findings from the other studies. Namely, a few prospective multicenter studies demonstrated that the %p2PSA and PHI have an improved prediction of clinically significant PC, both in men with a PSA between 4-10ng /mL and between 2-10ng/L (10-13, 15, 18). These biomarkers may therefore also have a role in monitoring men under active surveillance.

Some limitations of the present study need to be kept in mind in the interpretation of the results. First, this investigation was performed at a single institution, thus, results may not be generalizable to other health-care settings. However, the consecutive sampling design, in defined period of time, ensures the representativeness of the sample and the generalizability of the results. Secondly, cross-sectional design captures association but does not allow for causality or temporal sequence to be assessed. Moreover, keeping in mind the fact that group of patients without PC was also selected from the cohort of patients who visited the urologist and underwent prostate biopsy during the period of investigation, some kind of selection bias could also be introduced. Nevertheless, such kind of sampling to assess predictive value of different tumor markers in detection of patients with aggressive PC (assumed as Gleason score ≥7) in a subcohort of men whose total PSA ranged from 2 to 10ng/mL, supported the investigated hypothesis. Finally, agressivness of the PC has been estimated only by assessing the Gleason score which is only one of the criteria for the aggresive

tumor potential. It is clear that more comprehensive estimation of tumor-related agressiveness should include other parametes such as: number of sections with cancer, percentage of cancer in a single section etc (27, 28).

CONCLUSIONS

Derivates of p2PSA, PHI and especially %p2PSA, represented potentially very important clinical tools for predicting presence of PC in a cohort of Serbian males. Even more, these new markers could discriminate patients with Gleason score <7 from those Gleason score ≥7, within total PSA ranging from 2 to 10ng/mL. Those findings are central to avoid over diagnosis and subsequent over treatment.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Laparoscopic radical cystectomy with novel orthotopic neobladder with bilateral isoperistaltic afferent limbs: initial experience

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ABSTRACT

Purpose: To introduce a new method of constructing an orthotopic ileal neobladder with bilateral isoperistaltic afferent limbs, and to describe its clinical outcomes.
Materials and Methods: From January 2012 to December 2013, 16 patients underwent a new method of orthotopic ileal neobladder after laparoscopic radical cystectomy for bladder cancer. To construct the neobladder, an ileal segment 60cm long was isolated approximately 25cm proximally to the ileocecum. The proximal 20cm of the ileal segment was divided into two parts for bilateral isoperistaltic afferent limbs. The proximal 10cm of the ileal segment was moved to the distal end of the ileal segment for the right isoperistaltic afferent limb, and the remaining proximal 10cm ileal segment was reserved for the left isoperistaltic afferent limb. The remaining length of the 40cm ileal segment was detubularized along its antimesenteric border to form a reservoir. The neobladder was sutured to achieve a spherical configuration.
Results: All procedures were carried out successfully. The mean operative time was 330 min, mean blood loss was 328mL, and mean hospital stay was 12.5 days. The mean neobladder capacity 6 and 12 months after surgery was 300mL and 401mL, respectively. With a mean follow-up of 22.8 months, all patients achieved daytime continence and 15 achieved nighttime continence. The mean peak urinary flow rate was 11.9mL/s and 12.8mL/s at 6 and 12 months postoperatively, respectively.
Conclusions: This novel procedure is feasible, safe, simple to perform, and provides encouraging functional outcomes. However, comparative studies with long-term follow-up are required to prove its superiority.

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INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the most effective treatment for patients with organ-confined, muscle-invasive, or recurrent high-grade bladder cance (1). Recent advances in the development of laparoscopic instruments, improvements in surgical techniques, and improved surgical confidence and skills now allow the application of laparoscopy to diseases of the pelvic organs, including malignant disease and cases requiring complex reconstruction (2, 3).

Laparoscopic RC (LRC) using a variety of urinary diversion methods has been shown to be feasible and safe, and to be associated with many intraoperative and postoperative advantages (4-6). Various options are available for urinary

diversion, among which the orthotopic neobladder has several advantages, including near-normal voiding mechanics, elimination of the need for external appliances, preservation of body image, and superior quality of life (7).

Preservation of renal function is of paramount importance following urinary diversion. It is therefore important to reconstruct the orthotopic low-pressure neobladder so as to reduce long-term impairment of renal function. Here we report on our surgical techniques and preliminary results in 16 patients using LRC with a novel orthotopic ileal neobladder with bilateral isoperistaltic afferent limbs.

MATERIALS AND METHODS

Patient selection and preparation

Between January 2012 and December 2013, a total of 16 consecutive patients (15 males and 1 female) underwent LRC with a new orthotopic ileal neobladder with bilateral isoperistaltic afferent limbs in our institution.

The indications and exclusion criteria for LRC and orthotopic neobladder followed the 2012 guidelines of the Chinese Urological Association (8). Indications included: muscle-invasive bladder cancer stage T2–4a, N0–Nx, M0

- high-risk and recurrent non-muscle-invasive tumors
- bladder cancer stage T1G3
- extensive non-muscle-invasive disease that could not be controlled by transurethral resection and intravesical therapy.

Exclusion criteria included

- patient refusal of LRC
- the presence of contraindications to LRC, including distant metastasis; an American Society of Anesthesiologists (ASA) score >3; severe cardiac insufficiency; and decompensated pulmonary function that made the patient unable to tolerate pneumoperitoneum
- the presence of contraindications to neobladder, including tumor in the urethra, urethral stricture, abnormal abdominal straining, and decompensated renal function.

Out of the total of 16 patients, 8 presented with a primary bladder tumor and 8 with recurrent disease. All had had previous transurethral resection of the bladder tumor and intravesical chemotherapy. In our female case, the radical cystectomy included removal of the bladder, uterus, and distal ureters (9). The patient had pelvic lymphadenopathy indicated through CT preoperatively; we performed the extended PLND, and the pathological result was negative. All patients were diagnosed by cystoscopy and tumor biopsy. No distant metastasis was identified in any patient. Patients were evaluated preoperatively with cystoscopy, tumor biopsy, intravenous urography, ultrasonography, bone scan, computed tomography (CT), and/or magnetic resonance imaging (MRI).

All patients were determined by cystoscopy to be free of tumor in the urethra. Demographic and clinical parameters including age, sex, body mass index (BMI), ASA score, and clinical stage were assessed. Perioperative data were analyzed, including operative time, estimated blood loss, tumor size and histopathology, along with the incidence of complications.

All patients underwent bowel preparation by oral self-administration of 4L polyethylene glycol with electrolytes the day before the surgical procedure. On the morning of surgery, broad-spectrum intravenous antibiotics were administered. Compression stockings were applied to the lower extremities before induction of anesthesia in order to prevent deep vein thrombosis.

Surgical technique

Laparoscopic radical cystoprostatectomy or radical cystectomy was performed in all male and 1 female patients, respectively, followed in all patients by pelvic lymphadenectomy.

Patient positioning and port placement

General anesthesia was administered by tracheal intubation. The patient was placed in a supine steep Trendelenburg position and a nasogastric tube was inserted. A 16Fr Foley catheter was positioned, and 50mg epirubicin was perfused immediately for intravesical chemotherapy before the operation.

Pneumoperitoneum was obtained with a Veress needle. A primary 10mm laparoscopic trocar was placed at the level of the umbilicus. After inspection of the abdominal cavity, 4 other trocars were placed in a fan-shape. Two 12mm trocars were placed in ports 2cm below the umbilicus on the mid-clavicular line on both sides, and two 5mm trocars were placed 2–3cm superior and medial to the anterior superior iliac spines on each side.

Laparoscopic radical cystoprostatectomy

Our procedure comprised the following10 steps:

1. The adhesion between the sigmoid colon and the pelvis was dissociated, and the left ureter was mobilized.
2. The right ureter was mobilized.
3. A transverse peritoneotomy was made in the Pouch of Douglas.
4. The ampullae of the vas deferens were transected bilaterally, and the seminal vesicles were dissected and maintained en bloc with the bladder. Denonvillier's fascia was incised, and Denonvillier's space between the rectum and the prostate was developed as far as the apex of the prostate.
5. The anterior bladder wall and the space of Retzius were exposed.
6. The endopelvic fascia were incised bilaterally.
7. The puboprostatic ligament was dissected, and the dorsal vein complex was suture-ligated.
8. The lateral pedicles of the bladder and the prostate were bilaterally divided with LigaSure® (Covidien, Dublin, Ireland) if the neurovascular bundle did not need to be preserved. Otherwise, the bladder and prostate lateral pedicles were divided with Hem-o-lok® (Teleflex Medical, Research Triangle Park, NC, USA), clips and scissors.
9. The prostatic capsule was incised from 0.5–1.0cm to the apex of the prostate, the urethra was dissociated, the catheter removed, and the proximal urethra was clipped with Hem-o-lok® to prevent leakage of urine. For absolute certainty, the prostatic capsule was reserved about 0.5–1.0cm from the apex of the prostate and the prostate and urethra were removed.
10. Both ureters were clipped and divided close to the bladder, and the distal ureteral margin was sent for frozen section evaluation. The proximal cut end of each ureter was temporarily occluded with clips to facilitate hydrostatic distension.

Bilateral pelvic lymph node dissection

After RC was accomplished, PLND was performed, beginning with right lymphadenectomy. The criteria of a standard PLND were carried out, namely bifurcation of the common iliac artery proximally, the genitofemoral nerve laterally, the circumflex iliac vein and lymph node of Cloquet distally, and the hypogastric vessels posteriorly, including the obturator fossa. The removal of the lymph nodes was performed using a small endobag. Extended PLND was performed if there were positive results from frozen lymph node evaluation or if CT or MRI indicated pelvic lymphadenopathy.

Orthotopic ileal neobladder with bilateral isoperistaltic afferent limbs

Through the 8cm midline incision, the ileum was extracted from the peritoneal cavity, manual end-to-end anastomosis was performed to restore the continuity of the ileum, and the mesenteric window was closed to prevent internal hernia.

To construct the neobladder, an ileal segment 60cm long was isolated 25cm proximal to the ileocecum. The proximal 20cm of the ileal segment was divided into 2 parts for bilateral isoperistaltic afferent limbs. The proximal 10cm of the ileal segment was moved to the distal end of the ileal segment for the right isoperistaltic afferent limb, and the remaining proximal 10cm ileal segment was reserved for the left isoperistaltic afferent limb. Then, the remaining length of the 40cm ileal segment was detubularized along its antimesenteric border. The posterior wall of the neobladder was closed by continuous suturing of

adjacent detubularized ileal walls using 2-0 Vicryl suture. The anterior wall of the neobladder was folded forward and the free edges were sutured to achieve a spherical configuration (Figure-1).

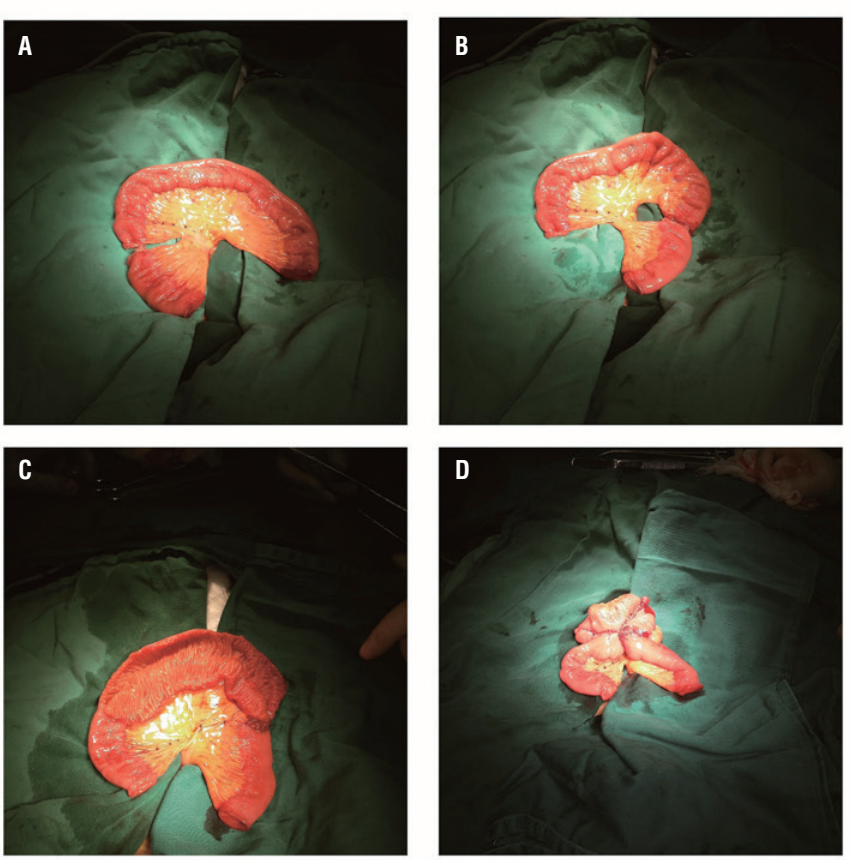
Before completing the suture of the neobladder, bilateral 6Fr ureteral single-J stents were delivered into the bilateral renal pelvis through the urethra, neobladder, limbs and ureters. The ureters were spatulated for about 1.5cm and the ureters were end-to-end anastomosed with the ipsilateral limb in a continuous manner using two separate 3-0 Vicryl sutures for each ureter. Sutures were used for the posterior and anterior walls. In this procedure, unlike in other types of urinary diversion, none of the ureter needed to be tunneled under the mesosigmoid to the contralateral side.

The neobladder was brought into the pelvis, and the urethra-ileal anastomosis was completed using a running suture intracorporeally. A 22Fr Foley catheter was then positioned.

Postoperative care

The reservoir was irrigated with 1.6% sodium bicarbonate solution and gentamicin saline with aspiration of the mucus through the Foley catheter every 4h starting on postoperative day 3. The tubal drains were removed after fluid drainage had ceased. The ureteral stents were removed 11–14 days after surgery. The urethral catheter was maintained for 15 days, a pouchography was performed, and the urethral catheter was removed if there was no extravasation.

Figure 1 – A) The orthotopic ileal neobladder with bilateral isoperistaltic afferent limbs. The proximal 20 cm of the ileum was divided into 2 segments for the bilateral isoperistaltic afferent limbs. B) The proximal 10 cm ileal segment was moved to the right side. C) The remaining 40 cm long segment was cleaned and detubularized along its antimesenteric border. D) The anterior wall of the neobladder was folded forward and the free edges were sutured to achieve a spherical configuration.



Patients were instructed to void while sitting after removal of the urethral catheter to facilitate good pouch evacuation. The voiding interval was gradually increased from 2 to 4h. The goal was a final bladder capacity of 400–500mL with urinary continence after 12 months.

Follow-up

Postoperative follow-up was conducted at 3-month intervals during the first year, at 6-month intervals during the second year, and annually thereafter.

Follow-up visits consisted of a history, physical examination, and routine biochemical profile. Ultrasonography of the abdomen, urography and chest x-rays were performed at 3, 6 and 12 months postoperatively, then annually unless otherwise clinically indicated. Abdominal/pelvic CT scans were performed 6 months postoperatively and annually thereafter.

Radiographic studies to evaluate the upper urinary tract included excretory urography, CT and renal ultrasonography. Serum determination of blood urea nitrogen and creatinine along with routine chemistry studies were performed at each follow-up visit.

The estimated glomerular filtration rate (eGFR) was calculated preoperatively and at various intervals after surgery. It was calculated with an equation developed by adaptation of the Modification of Diet in Renal Disease (MDRD) equation on the basis of data from Chinese chronic kidney disease patients (10).

Continence status and voiding pattern were determined by telephone interview. Continence was strictly defined as good if the patient was completely dry without the need for any protection, satisfactory if no more than 1 pad was required during the day or night, and unsatisfactory if the patient was using more than 1 pad during the day or night. The voiding pattern was classified as: being able to void to completion without the need for catheterization; requiring any form of intermittent catheterization for residual urine; or being unable to void and requiring continuous intermittent catheterization.

RESULTS

Patient demographic and perioperative data are presented in Table-1. There were 15 men and 1 woman with a mean age of 65 years (range: 54–77 years) and a mean BMI of 25.0 (range: 21.3–28.1). The mean ASA score was 2.3. All procedures were carried out successfully without conversion to open surgery. The mean operative time was 330 min (range: 260–410 min). The mean estimated blood loss was 328mL (range: 200–600mL), and 1 (6%) patient required transfusion.

Patients were ambulatory on postoperative day 1 or 2, and the mean time to resumption of oral intake was 4.9 days (range: 4–6 days). The drainage tube was removed at a mean of postoperative day 8.1 (range: 6–11 days), the bilateral ureteral stent was removed on postoperative day 14, and the Foley catheter was removed on postoperative day 14 or later. The mean hospital stay was 12.5 days (range: 10–16 days).

Complications

Complications were graded according to the modified Clavien classification system (11). In this series, we observed 6% (1/16), 13% (2/16) and 6% (1/16) intraoperative, early (≤30 days) and late complications (≤90 days), respectively (Table-1). All early and late complications were minor complications (grade I–II). Complications were mostly related to the orthotopic neobladder urinary diversion. The obturator nerve was injured in one case, but laparoscopic nerve anastomosis was carried out successfully and the patient recovered without any dysfunction.

Neobladder function

At 12 months postoperatively, the daytime and nighttime continence rates of the 15 male patients were 100% (15/15) and 93% (14/15), respectively. One patient used small/mini pad at night. The pouch capacity and the residual volume were measured by ultrasonography. The mean maximal pouch capacity was 297mL (range: 200–410mL) and 400mL (range: 345–480mL) at 6 and 12 months postoperatively, respectively. The mean residual volume was 16.6mL (range: 0–40mL) and 28mL (range: 0–60mL)

Table 1 - Demographics and surgical outcomes.

Age mean±SD (range), year	64.8±6.0 (54-77)
ASA mean±SD (range)	2.3±0.4(2-3)
Male, n (%)	15 (93)
BMI mean±SD (range), kg/m^2	25.0±1.8 (21.3-28.1)
Operative time mean±SD (range),min	330±47(260-410)
Estimated blood loss mean±SD (range), mL	328±113 (200-600)
Blood transfusion n (%)	1 (6)
Oral fluids intake time mean±SD (range), day	4.9±0.8 (4-6)
Drainage tube remove mean±SD (range), day	8.1±1.5 (6-11)
Hospital stay, mean±SD (range), day	12.5±1.6(10-16)
Complications,n	
Intraoperative complications	
Obturator nerve injured	1
Early complications (≤30 days)	
Urine leakage	1
Urinary infection	1
Late complications (≤90 days)	
Adhesive intestinal obstruction	1
Pathology results	
Transitional cell carcinoma n. (%)	15(94%)
Adenocarcinoma n. (%)	1(6%)
Number of pelvic lymph nodes	16.1±3.3 (8-22)
Patient with positive pelvic lymph node (%)	1(6%)
Follow-up median (range), month	26(16-39)

BMI = Body Mass Index; **ASA** = American Society of Anesthesiologists; **SD** = standard deviation.

at 6 and 12 months postoperatively, respectively. The mean peak flow rate was 11.5mL/s (range: 6.5–16.5mL/s) and 12.2mL/s (range: 8.8–17.2mL/s) at 6 and 12 months postoperatively, respectively.

The daytime and nighttime continence of the female patient was satisfied. The maximal pouch capacity was 350mL and 410mL at 6 and 12 months postoperatively, respectively. The residual volume was 20mL and 50mL at 6 and 12 months postoperatively, respectively. The peak flow rate was 20mL/s and 20.5mL/s at 6 and 12 months postoperatively, respectively (Table-2).

Pathology data

The pathology results are presented in Table-1. In this study, 15/16 (94%) patients had transitional cell carcinoma, and 1/16 (6%) patient had adenocarcinoma. The mean number of lymph nodes

Table 2 - eGFR, Urinary continence and neobladder function of 16 patients at postoperative 12 months.

eGFR (range), mL per minute/1.73 m²	
preoperatively	72.1±12.4(48.4-89.6)
postoperatively 12months	69.1±12.0(40.9-85.5)
Continence	
Day continence, n	16
Night continence, n	15
Satisfactory continence, n (%)	15(94%)
Total incontinence, n (%)	1(6%)
Neobladder functions	
Maximal pouch capacity mean (range), mL	401 (345-480)
Residual volume mean(range), mL	30 (0-60)
Peak flow rate mean(range), mL/s	12.8 (8.8-20.5)

removed was 16.1 (range: 8–22). Five patients who had high-grade transitional cell carcinoma and 1 patient with positive lymph nodes received adjuvant chemotherapy.

Follow-up and survival data

After a median follow-up of 22.8 months (range: 16–36 months), 12 patients were alive with no evidence of local recurrence or distant metastasis. Four patients were diagnosed as lung metastases and received adjuvant chemotherapy. One patient died 18 months postoperatively. The median eGFR was 72.1mL per minute/1.73m2 preoperatively and 69.1mL per minute/1.73m2, 1 year postoperatively. There was no deterioration in renal function in any of the patients during follow-up. The intravenous pyelogram and enhanced CT scan showed that no hydronephrosis had occurred (Figure-2).

DISCUSSION

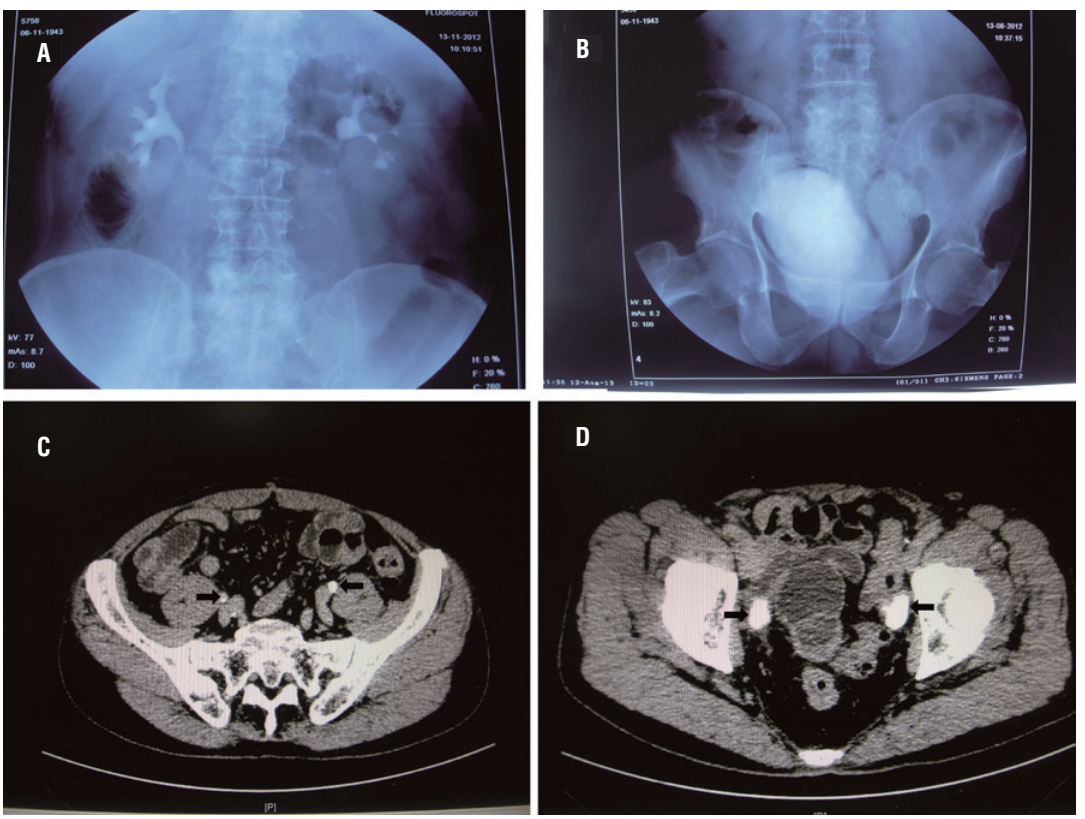
The advances that have been made in both the design of instruments and laparoscopic techniques have stimulated the development of laparoscopic surgery. Nowadays, LRC is considered to be a safe, feasible and minimally invasive alternative to RC with fewer overall complications, less blood loss, shorter length of hospital stay, shorter time to regular diet, and reliable pathologic and oncologic efficacy (12).

We reported our first laparoscopic radical cystectomy and urinary diversion in 2005, and since then more than 600LRCs have been performed by experienced surgeon Nianzeng Xing. Most of the neobladder reconstructions were performed extracorporeally through a 5–8cm incision.

Hautmann et al. initially reported an orthotopic low-pressure reservoir using detubularized ileum in 1988 (13). One year later, Studer et al. described a new technique using a long, afferent and isoperistaltic ileal segment for the construction of a neobladder with good functional results (14). In many institutional centers worldwide, orthotopic neobladder has now replaced the ileal conduit as the standard form of reconstruction.

Preservation of upper tract integrity and function is one of the essential requirements when a urinary bladder substitute is indicated. Following Hinman's principles (15), there is general agreement that detubularization of the bowel is required to nullify the pressure waves created by peristalsis and to obtain maximum capacity from a given length of bowel. Studer and coworkers proposed the use of an isoperistaltic long afferent loop for reflux prevention. They maintained that the unidirectional peristalsis of the ureters and the afferent tubular ileal segment sufficiently protected the upper urinary tracts following ileal bladder substitution up to a decade after urinary diversion (16).

Figure 2 - Image examinations from follow-up. A) An IVP showed the bilateral pelvis and ureters were normal and there were no appearance of hydronephrosis (POD 10 months). B) An IVP showed the shape of the neobladder. C) Delay phase of a enhanced CT scan showed there were no appearance of the dilation of the bilateral ureters (black arrows). D) Delay phase of the enhanced CT scan showed the appearance of the bilateral isoperistaltic afferent limbs (black arrows) and the neobladder.



However, the Studer pouch has only one afferent limb, which is anastomosed with bilateral ureters. The left ureter has to be tunneled under the mesosigmoid to the right side in order to be implanted in the afferent ileal part. In 2013, Studer et al. retrospectively evaluated the records of 74 patients treated for unilateral or bilateral non-malignant ureteroileal strictures, indicating that left ureteroileal strictures were almost twice as common as right strictures, and, compared with right strictures, they were significantly more often larger than 1cm (17). They concluded that the additional mobilization of the left ureter as it was brought to the right side could worsen the blood supply and thus lead to the development of ureteroileal stricture as a result of chronic ischemia.

In our study, the ureters were anastomosed with the ipsilateral limb of the neobladder without excessive mobilization. No patients developed an ureteroileal stricture during the 2-year follow-up, and this advantage should certainly be demonstrated by long-term follow-up. The rate of ureteroileal stricture was reduced because:

- there is no need for excessive mobilization and devascularization of the left ureter
- none of the ureter needs to be tunneled under the mesosigmoid to the contralateral side
- the diameter of the anastomosis is wide enough.

Stein and Skinner reported on the orthotopic T-pouch ileal neobladder incorporating a serosa-lined ileal antireflux technique and concluded that it is an extremely effective and versatile flap-valve method that can be applied to

the construction of continent urinary diversions (18). However, it is a complex surgical procedure and, in addition, the ureter has to be transposed. We have performed the T-pouch procedure since 2009. It is a good orthotopic neobladder with regard to offering good kidney protection and urinary continence, but it is too complicated, especially for intracorporeal construction.

Y-shaped orthotopic neobladder was reported by Fontana et al. (19). The procedure of Y--shaped neobladder construction was described as follows: the isolated intestinal segment was arranged in a Y-shape with 2 central segments of 14cm and two limbs of 6cm. The 2 central segments were brought together and detubularized. The ureters were directly anastomosed to the open ends of the limbs of the neobladder. The Y-shaped neobladder is quite different from our neobladder. One important difference is our pouch is a true globularized neobladder with increased capacity and decreased pressures. Furthermore, our pouch has bilateral isoperistaltic afferent limbs, whereas although the Y-shaped neobladder has bilateral afferent limbs, only one of the limbs is isoperistaltic.

In 2002, Gill et al. first reported their initial clinical experience with LRC with intracorporeal orthotopic ileal neobladder in 2 patients (20). Since then, the robotic-assisted approach is most commonly used in intracorporeal neobladder construction.

In 2015, Shao et al. presented their experience of LRC with intracorporeal orthotopic ileal neobladder in 50 cases (21). However, it still does not use a special neobladder construction for intracorporeal approach. Our novel orthotopic neobladder can be carried out purely laparoscopically. We began to perform LRC and intracorporeal neobladder construction with this neobladder last year. The results are encouraging, and will be reported later.

Monitoring both eGFR and postoperative hydronephrosis permitted early detection of urinary obstruction. Prompt surgical treatment prevented renal deterioration in this subgroup of patients. In our study both the eGFR and imaging showed the result were satisfied.

The main limitation of this study is the relatively small sample size, short follow-up time, and lack of control group. However, the aim of this study was to report our experience with constructing the novel neobladder as performed by one surgical team. A larger, multicenter, comparative study with long-term follow-up is needed to confirm its superiority.

This novel procedure is feasible and safe to perform with encouraging functional outcomes. It does not require removal of the left ureter to the right side to anastomose with the reservoir, and the ureters are sutured to the afferent limbs end--to-end. The bilateral isoperistaltic afferent limbs of the neobladder protect the morphology and function of the upper urinary tract.

Ethical Standards

The study received approval from the research ethics board of Chaoyang Hospital.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Can neutrophil to lymphocyte ratio predict lamina propria invasion in patients with non muscle invasive bladder cancer?

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ABSTRACT

Objective: Recent studies have demonstrated the role of systemic inflammation in the development and progression of cancer. In this study, we evaluated whether preoperatively measured neutrophil-to-lymphocyte ratio (NLR) can predict lamina propria invasion in patients with non-muscle-invasive bladder cancer (NMIBC).

Material and Methods: We reviewed the medical records of 304 consecutive and newly diagnosed patients with bladder cancer who had been treated with transurethral resection between January 2008 and June 2014. In total, 271 patients were included in the study and the patients were divided into two groups according to the pathological stage (Group 1: Ta, Group 2: T1). NLR was calculated by dividing the absolute neutrophil count (N) by the absolute lymphocyte count (L).

Results: In total, 271 patients (27 women and 244 men) were enrolled. Mean age was higher in Group 2 than in Group 1 (67.3±10.8 vs. 62.9±10.8, p<0.001). Furthermore, the presence of high grade tumors and tumors ≥3cm in size was statistically higher in Group 2 than in Group 1 (70.9% vs. 9.9%, p=0.0001; 71.8% vs. 36%, p=0.0001, respectively). While the mean white blood cell (WBC) and N counts were statistically insignificant (7.63±1.87 vs. 7.69±1.93, p=0.780; 4.72±1.54 vs. 4.46±1.38, p=0.140; respectively), L was significantly lower and NLR was significantly higher in Group 2 than in Group 1 (2.07±0.75 vs. 2.4±0.87, p=0.001; 2.62±1.5 vs. 2.19±1.62, p=0.029; respectively).

Conclusion: Our data indicate that high NLR and low L are statistically associated with T1 stage, whereas low L are able to predict lamina propria invasion in patients with NMIBC. These findings suggest that pretreatment measurement of NLR may provide valuable information for the clinical management of patients with NMIBC. Prospective studies are now required to further validate the role of NLR as a risk factor in NMIBC.

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INTRODUCTION

Bladder cancer is the most common urinary tract malignancy and the third most common cancer in men, following prostate and lung cancer, with an estimated 58.950 new cases and 11.820 deaths in 2016 alone (1). While 75%-85% of the patients with bladder cancer present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1), the remaining cases may often include bladder cancers that invade the muscle (2). Moreover, it is known that non-muscle-invasive bladder cancer (NMIBC) may progress as 43% of patients with muscle invasive bladder

cancer treated with radical cystectomy were initially diagnosed with NMIBC (3). Therefore, identifying NMIBC patients in whom the cancer is more likely to progress is an important issue to consider for in the management of these patients. A risk Table published by the European Organization for Research and Treatment of Cancer (EORTC) previously suggested stratifying patients into low-, intermediate-, and high-risk groups, a strategy designed to help guide the management of these patients (4).

Recent studies have demonstrated the role of systemic inflammation in the development and progression of cancer (5). For example, an elevated neutrophil-to-lymphocyte ratio (NLR) has consistently been found to be associated with muscle--invasive disease, extravesical disease, along with worse overall and disease-free survival rates (6-9). Recently published data have also revealed that an elevated NLR is an independent predictor of disease progression and recurrence in patients with NMIBC (10). The aim of the current study was to evaluate whether preoperatively measurement of NLR can predict lamina propria invasion in patients with NMIBC.

MATERIAL AND METHODS

This study was approved by the local ethics committee. We retrospectively reviewed the medical records of 304 consecutive and newly diagnosed patients with non muscle invasive bladder cancer treated with transurethral resection between January 2008 and June 2014. Patients with preoperative infection, hematological malignancies and unexplained leukocytosis (n=33) were excluded from the study. Patients were divided into two groups according to their pathological stage (Group 1: Ta, n=161; Group 2: T1, n=110). From each patient, we obtained preoperative blood data including white blood cell (WBC), neutrophil (N) and lymphocyte counts (L). NLR was calculated by dividing N by L. The size and number of tumors were determined using preoperative radiological imaging and cyctoscopic examination prior to transuretral resection. Groups were then compared with regard to age, gender, tumor size, tumor number, WBC, N, L, and NLR.

Statistical analyses

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS) (2007, Utah, USA). Categorical variables were summarized using actual counts and percentages, whereas continuous variables were summarized using the mean±SD. Parametric and non parametric variables were evaluated using the t-test and chi-squared test, respectively. Logistic regression analysis was also used to determine predictors of T1 stage tumors. Statistical significance was considered at $p<0.05$.

RESULTS

In total, 271 patients were enrolled in this study (27 women and 244 men). Mean age was higher in Group 2 than in Group 1 (67.3±10.8 vs. 62.9±10.8, $p<0.001$). The incidence of high grade tumors and tumors ≥3cm in size was statistically higher in Group 2 than in Group 1 (70.9% vs. 9.9%, p=0.0001; 71.8% vs. 36%, p=0.0001, respectively). While the mean WBC and N counts were statistically insignificant (7.63±1.87 vs. 7.69±1.93, p=0.780; 4.72±1.54 vs. 4.46±1.38, p=0.140; respectively), L was significantly lower and NLR was significantly higher in Group 2 than in Group 1 (2.07±0.75 vs. 2.4±0.87, p=0.001; 2.62±1.5 vs. 2.19±1.62, p=0.029; respectively) (Table-1).

In order to evaluate the factors that might affect the presence of T1 tumors, we performed logistic regression analysis. High grade tumor (p=0.001), tumor size (≥3cm) (p=0.001), and L (p=0.049) were all associated with T1 tumors (Table-2).

According to the receiver operating characteristic analysis, the optimum cut-off value for NLR and L was >1.84 (area under curve [AUC] 0.616, 95% CI, 0.556-0.675) and ≤2.4 ([AUC] 0.625, 95% CI, 0.564-0.683), respectively (Figure-1). Sensitivity for NLR and L was 67.3% vs. 75.5%, whereas specificity was 54.1% vs. 47%, respectively (Table-3).

DISCUSSION

Non-muscle invasive bladder cancer represents a heterogeneous group of tumors with di-

Table 1 - Patients characteristics.

			Group 1 (Ta, n:161)		Group 2 (T1, n:110)	p
Age			62.9±10.8		67.3±10.77	0.001¥
Gender	Man (%)	146	90.7%	98	89.1%	
	Woman (%)	15	9.3%	12	10.9%	0.667□
Grade	PUNLMP (%)	51	31.7%	2	1.8%	
	Low Grade (%)	94	58.4%	30	27.2%	
	High Grade (%)	16	9.9%	78	70.9%	0.0001□
Tumor Size	<3 cm (%)	103	64%	31	28.2%	
	≥3 cm (%)	58	36%	79	71.8%	0.0001□
Tumor Number	Single Tumor (%)	107	66.5%	68	61.8%	
	Multiple Tumor (%)	54	33.5%	42	38.2%	0.443□
WBC (mean±sd)			7.69±1.93		7.63±1.87	0.780¥
Neutrophil (mean±sd)			4.46±1.38		4.72±1.54	0.140¥
Lymphocyte (mean±sd)			2.4±0.87		2.07±0.75	0.001¥
NLR (mean±sd)			2.19±1.62		2.62±1.5	0.029¥

PUNLMP = Papillary urothelial neoplasm of low malignant potential
WWBC = White blood cell; **NLR =** Neutrophil-to-lymphocyte ratio.

¥ = Independent sample t test; □ = chi-square test

Table 2 - Logistic regression analyses for predicting T1 tumors.

	B	S.E.	p	OR	OR %95 CI	
					Lower	Upper
Grade			**0.001**			
Grade (Low Grade)	-4.63	0.78	**0.001**	0.01	0.00	0.05
Grade (High Grade)	2.62	0.36	**0.001**	0.07	0.04	0.15
Tumor size (≥3cm)	1.21	0.35	**0.001**	0.30	0.15	0.59
Lymphocyte	-0.41	0.21	**0.049**	0.66	0.44	1.00

fferential rates of recurrence and progression (11). The risk of progression primarily depends on the tumor grade, number, and size of tumor (12). Recently published data showed that the EORTC risk model is useful in predicting the progression of NMIBC but also noted the importance of updating new risk markers to improve the risk classification and prediction of progression (13). The current study assessed the predictive value of preoperative blood tests for lamina propria invasion in patients with NMIBC who were treated with TUR. Our analyses showed that low L (≤2.4) can

act as an effective predictor for T1 tumors. While NLR was unable to predict T1 tumors with statistical probability, NLR was statistically higher in patients with T1 tumors than in patients with Ta tumors. Furthermore patients with NLR >1.8 exhibited a risk of developing a T1 tumor that was 1.5 times greater.

Increasing evidence supports the involvement of systemic inflammation in the growth and progression of tumors (5). NLR, is a parameter of stress and systemic inflammation, which is readily measurable in substantially ill patients (14). The association of pretreatment NLR and prognosis has also been reported for various other types of cancer, including ovarian cancer, gastric cancer, hepatocellular carcinoma, non-small cell lung cancer, and bladder cancer (15-20). Moreover, preoperative NLR was found to be associated with the progression and recurrence of NMIBC (7, 10, 20).

The relationships between increased NLR, and poor prognosis, and advanced stage of tumor can be explained by the impaired immune response of hosts to the tumor, which is dependent on L (14). Tumor proliferation and the survival of malignant cells ultimately depend on inflammation in the tumor microenvironment, and inflammation is also known to stimulate tumor angiogenesis, invasion, and metastasis (5). In advanced cancer patients, a variety of biological factors such as leukocytosis, lymphocytopenia, and C-reactive protein have been identified as having a definite correlation with prognosis (21). Because neutrophils inhibit the immune system and lymphocytes have a role in cell-mediated immunity in the host, such cellular components may reflect the host inflammatory and immune response (22). This hypothesis was confirmed by the fact that we observed a lower L among patients with T1 tumors in the present study.

As a result of exposure to carcinogens, the accumulation of mutations, and a reduction in immune function, the incidence of cancer and the prevalence of more advanced tumor stages are more common in elderly patients (23). Aged patients are susceptible to a range of changes that serve to di-

Figure 1 - Assesment of cut off value of neutrophil-to-lymphocyte ratio and lymphocyte counts to predict T1 tumors.

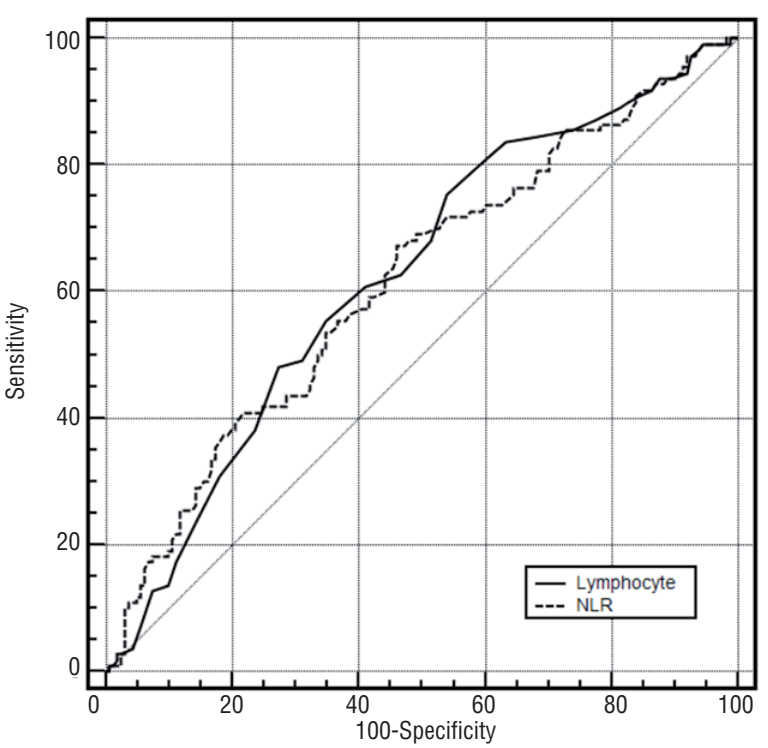

Table 3 - Sensitivity and specificity for NLR and lymphocyte.

Cut off	Sensitivity	Specificity	PPV	NPV	+LR
> 1.84 NLR	67.27	54.04	50.0	70.7	1.46
≤ 2.4 Lymphocyte	75.45	46.96	48.8	73.3	1.40

NLR = Neutrophil-to-lymphocyte ratio; **PPV =** Positive predictive value; **NPV =** Negative predictive value.

minish immune function such as a reduction in the number of functional B and T cells, modifications in the production and secretion of cytokines, reduced cytotoxic activity of $CD8^+$ T cells, qualitative deficiency of B lymphocytes with reduced response to exogenous antigens, decline in the activity of natural killer cells, and possibly a deficiency in antigen-presenting cells (23). On the other hand, age does not appear to influence L (24). These circumstances indicate that the differences observed between our two study groups in terms of L and NLR cannot be explained by only age.

To the best of our knowledge this is the first study that evaluated whether preoperative measurement of NLR can predict lamina propria invasion in patients with NMIBC and demonstrated that NLR is statistically higher in T1 tumors than Ta. Moreover, low L counts can predict lamina propria invasion in NMIBC. Our results are likely to be beneficial to surgeons when explaining the risk of progression to patients with NMIBC prior to surgery.

The limitations of our present study include its retrospective nature and the relatively small number of patients studied. These factors may reduce the reliability of our preoperative results. Furthermore, the two groups being compared were statistically different in terms of age. This difference could be considered as a form of selection bias, although we suggest that this difference simply reflects the very nature of bladder cancer as it is well known that advanced age is related to advanced stages of bladder cancer. Moreover, the tumor characteristics were not well described in the operation notes and we had many missing data when we evaluated TURB records. Therefore, we used preoperative radiological imaging and cystoscopic examination together instead TURB records alone.

CONCLUSIONS

The present study has indicated that high NLR and low L are associated with T1 stage, whereas a low L is able to predict lamina propria invasion in patients with NMIBC. These findings suggest that pretreatment NLR and L may provide valuable information in the clinical management of patients with NMIBC. Prospective studies between comparable groups are now required to validate the precise role of NLR as a potential risk factor for NMIBC.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Myiasis associated with penile carcinoma: a new trend in developing countries?

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ABSTRACT

Objectives: The aim of this study is to report an unusual form of penile cancer presentation associated with myiasis infestation, treatment options and outcomes.
Materials and Methods: We studied 10 patients with suspected malignant neoplasm of the penis associated with genital myiasis infestation. Diagnostic assessment was conducted through clinical history, physical examination, penile biopsy, larvae identification and computerized tomography scan of the chest, abdomen and pelvis. Clinical and pathological staging was done according to 2002 TNM classification system. Radical inguinal lymphadenectomy was conducted according to the primary penile tumor pathology and clinical lymph nodes status.
Results: Patients age ranged from 41 to 77 years (mean=62.4). All patients presented squamous cell carcinoma of the penis in association with myiasis infestation caused by *Psychoda albipennis*. Tumor size ranged from 4cm to 12cm (mean=5.3). Circumcision was conducted in 1 (10%) patient, while penile partial penectomy was performed in 5 (50%). Total penectomy was conducted in 2 (20%) patients, while emasculation was the treatment option for 2 (20%). All patients underwent radical inguinal lymphadenectomy. Prophylactic lymphadenectomy was performed on 3 (30%) patients, therapeutic on 5 (50%), and palliative lymphadenectomy on 2 (20%) patients. Time elapsed from primary tumor treatment to radical inguinal lymphadenectomy was 2 to 6 weeks. The mean follow-up was 34.3 months.
Conclusion: The occurrence of myiasis in the genitalia is more common in patients with precarious hygienic practices and low socio-economic level. The treatment option varied according to the primary tumor presentation and clinical lymph node status.

ARTICLE INFO

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INTRODUCTION

Penile cancer is a rare neoplasm which treatment causes devastating effects on the patient's physical and mental health. The low incidence of this disease in developed countries in contrast to the high incidence in developing countries clearly indicates the disease's association with local economic conditions (1-4). Although in the United States the incidence rate of penile cancer accounts for 0.2 cases per 100.000 inhabitants, in Brazil this rate ranges from 2.9 to 6.8 per 100.000 inhabitants. As a result, Brazil is ranked as one of the countries with the highest incidence of this neoplasia in the World (4, 5).

There are few epidemiological studies conducted in patients with penile carcinoma (4, 5). In a recent series, the authors established an epidemiological profile in which patients had a very low socio-economic status with low education, tending to delay seeking medical help, and therefore the diagnosis of the disease is frequently performed in advanced stages (5).

Myiasis is defined as a disease caused by the infestation of larvae or maggots of numerous flies species that grow inside a host, while feeding on the host's tissue. Such flies are usually attracted to open wounds and urine or feces-soaked fur (6). The incidence of myiasis is more commonly observed in rural areas as well as socioeconomically underdeveloped regions with precarious hygiene conditions (6, 7). The occurrence of myiasis in the genitalia is rare (7), especially when linked to penile cancer (8).

The aim of this study is to report an unusual form of penile cancer presentation associated with myiasis infestation, treatment options, and outcomes.

MATERIALS AND METHODS

Between January 2003 and July 2014, 10 patients with suspected malignant neoplasm of the penis associated with genital myiasis infestation were admitted in our emergency room facility (Figures 1 and 2). Primary diagnostic assessment was conducted through clinical history and physical examination. All patients presented genital tissue infection and were primarily treated with a combination of venous antibiotics (Ciprofloxacin and Clindamycin), started on hospital admission, totaling 21 days, and oral single dose of Ivermectin (150mcg/Kg) for parasitic infection. All patients underwent larvae manual removal and biopsy of the primary lesion for diagnostic confirmation under anesthesia. Larvae taken from the primary penile tumor were sent to the laboratory for classification.

Epidemiological variables evaluated in this study were: age, ethnicity, educational level, smoking, presence of phimosis, practice of circumcision and clinical history of sexually transmitted diseases.

Patients were clinically evaluated for the presence of inguinal and visceral metastases by physical examination of the inguinal region and computerized tomography scan of the chest, abdomen and pelvis. Clinical and pathological staging was done according to 2002 TNM classification system. Clinical characteristics of the primary lesion as well as the clinical TNM classification are described in Table-1.

Pathological material was reviewed and all tumors were histologically classified based on Broder's system. Only two pathologists were responsible for reviewing the primary penile lesions and lymphadenectomy specimens. The pathological variables studied were the histological type, grade, size of the lesion, corpus spongiosum and/or corpora cavernosa infiltration, urethral infiltration, and lymphovascular involvement.

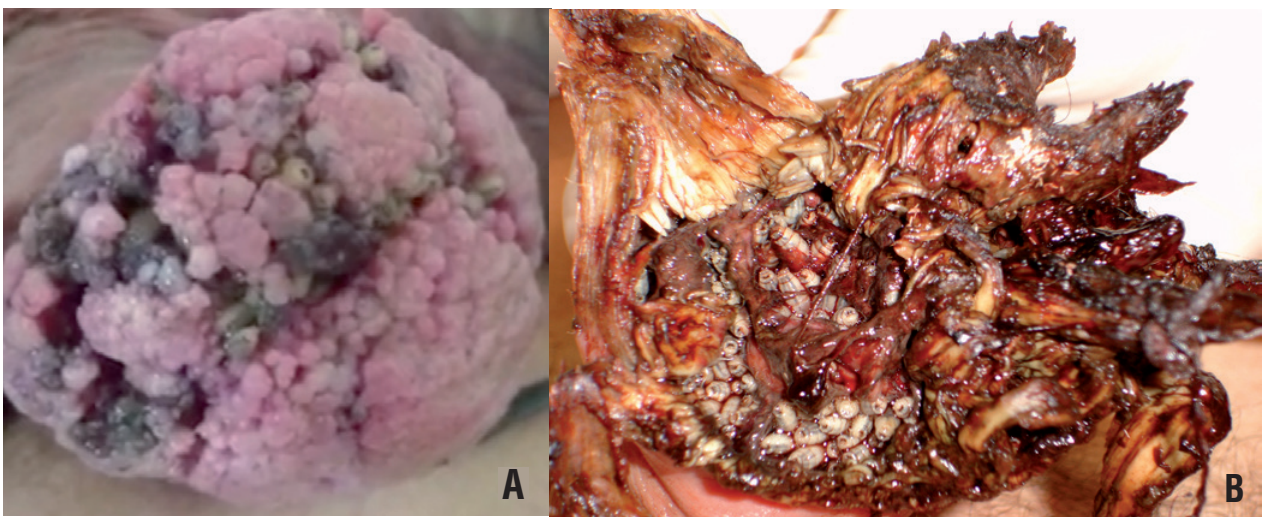
The type of treatment for the primary tumor of each patient was included in this study. All patients who were indicated for adjunctive treatment of inguinal lymphatic basins underwent radical bilateral inguinal lymphadenectomy. We considered lymphadenectomy to be prophylactic when performed on patients with clinically negative lymph nodes and high risk of inguinal dissemination (PT2 and/or lymphovascular invasion and/or Broders histological classification greater than or equal to II). We considered it to be therapeutic when performed on patients with clinically positive inguinal lymph nodes. Finally, we considered it to be palliative for patients with large ulcerated tumor masses and/or masses fixed in the inguinal region. The time elapsed from the primary tumor treatment and radical inguinal lymphadenectomy was evaluated.

All patients were evaluated prospectively and provided informed consent to participate in the study. Our institutional review board also approved the study. The mean follow-up was 34.3 months.

RESULTS

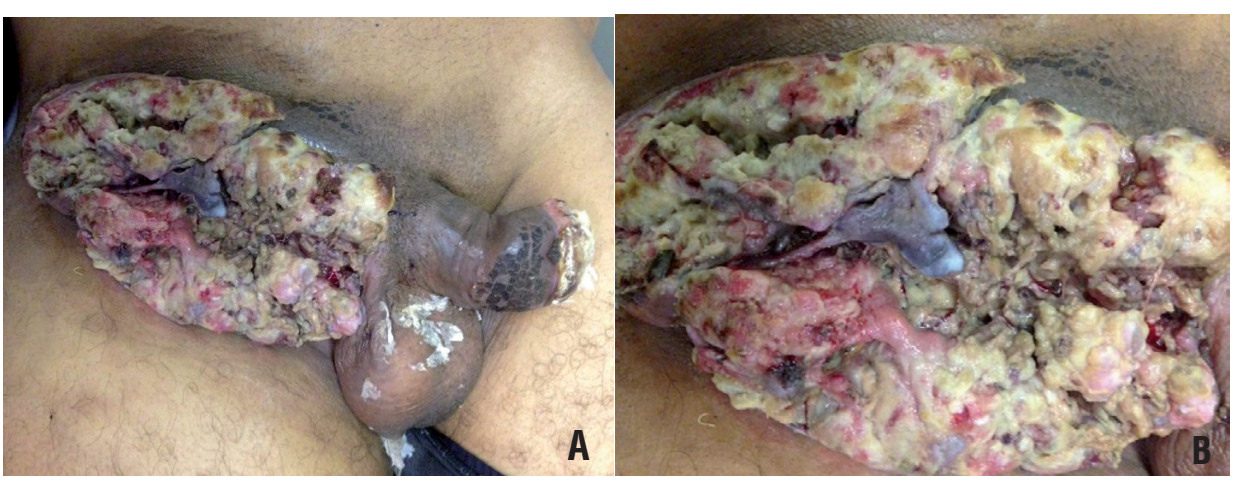
Patient's age ranged from 41 to 77 years (mean=62.4). Of the 10 patients evaluated, 9 (90%) were white and 1 (10%) black. The level of education varied from illiterate in 8 (80%) patients, to high-school graduate in 2 (20%) patients.

Figure 1 - Penile cancer associated to myiasis. A) 44 year-old patient with extensive lesion in penile shaft with secondary infection associated with myiasis infestation.



(Added with permission of Int Braz J Urol).

Figure 2 - Penile cancer associated to inguinal myiasis. A) We can observe a 60 year-old patient with extensive inguinal metastasis due to penile cancer. B) In high magnification we can observe the inguinal metastasis infested by myiasis.



Among the evaluated patients, 8 (80%) were homeless while 2 (20%) lived in supported geriatric home. In this series, all patients were tobacco smokers and only 1 (10%) had been circumcised in adolescence. The remaining 9 (90%) patients presented phimosis. Only 2 (20%) patients reported history of sexually transmitted diseases, presented as urethritis. The remaining 8 (80%) patients were not able to report or denied sexually transmitted diseases.

In relation to the pathological variables studied, all patients presented squamous cell carcinoma of the penis. The lesion size ranged from 4cm to 12cm (mean=5.3). The treatment option for the patients varied according to the presentation of the primary tumor (Table-1). Circumcision with partial amputation of the glans was conducted in 1 (10%) patient while partial penectomy was performed in 5 (50%) patients. Total penectomy was conducted in 2 (20%) patients while emasculation was the treatment option for 2 (20%) patients with extensive involvement of the penile shaft and scrotum. All patients underwent

Table 1 - Clinical characteristics of primary lesion, patient's age, anatomical area of myiasis infestation, primary tumor location, and clinical 2002 TNM classification.

Age	Tumor Location	Area of Myiasis	Clinical Characteristics Primary Lesion	TNM
41	Glans and Penile Shaft	Glans	8 cm exophytic lesion with gross inflammatory and infectious signs	CT3N1M0
55	Glans, Penile Shaft and Scrotum	Penile shaft	12 cm genital lesion involving glans and penile shaft with extensive ulcerated area with gross inflammatory and infectious signs	CT4N2M0
65	Glans and Penile Shaft	Glans and Penile Shaft	7 cm ulcerated lesion with gross inflammatory and infectious signs	CT3N1M0
60	Glans, Penile Shaft and Scrotum	Glans, Penile Shaft, Scrotum and Inguinal Area	7 cm exophytic lesion with gross inflammatory and infectious signs	CT4N3M0
62	Glans	Glans and Inguinal Area	4 cm exophytic lesion with gross inflammatory and infectious signs	CT3N3M0
67	Prepuce and Glans	Prepuce and Glans	5 cm ulcerated lesion with gross inflammatory and infectious signs	CT2N0M0
72	Prepuce and Glans	Prepuce and Glans	5 cm exophytic lesion with gross inflammatory and infectious signs	CT2N0M0
70	Prepuce and Glans	Prepuce and Glans	4,5 cm exophytic lesion with gross inflammatory and infectious signs	CT2N0M0
55	Prepuce and Glans	Prepuce and Glans	4 cm exophytic lesion with gross inflammatory and infectious signs	CT2N2M0
77	Prepuce and Glans	Prepuce and Glans	5 cm exophytic lesion with gross inflammatory and infectious signs	CT2N2M0

bilateral inguinal radical lymphadenectomy to complement the treatment of the primary lesion. Prophylactic lymphadenectomy was carried out on 3 (30%) patients while therapeutic lymphadenectomy was conducted on 5 (50%) patients. The remaining 2 (20%) patients were submitted to palliative lymphadenectomy. Chest, abdomen, and pelvis computerized tomography done systematically to stage all cases revealed no visceral metastasis or pelvic lymphadenopathy suggesting tumor spread. Time elapsed from primary tumor treatment to inguinal lymphadenectomy was 2-6 weeks in 5 (50%) patients while in 5 (50%) remaining patients, both procedures were performed simultaneously.

The larvae collected from the penile tumors and sent to the laboratory were classified as *Psychoda albipennis*, a species from the family *Psychodidae* and gender *Psychoda*. Treatment for parasitic infestation was effective with no detected larvae in surgical specimens.

Pathological characteristics of the primary penile tumor and lymph node are represented in Table-2.

DISCUSSION

Urogenital myiasis is an extremely rare condition seen in immunocompromised individuals, elderly, and persons with poor personal hygiene. It commonly occurs in tropical, subtropical countries, and areas with warm climate (9-11).

The most common form of myiasis in men takes place in the skin, where the species Dermatobia hominis is mostly observed. The severity of the condition depends on the location and on

Table 2 - The table shows the pathological features and surgical stage according to 2002 TNM classification of the 10 patients with penile cancer associated to myiasys.

	TUMOR STAGE			
Pathologycal features	**pT1 (%)**	**pT2 (%)**	**pT3 (%)**	**pT4 (%)**
G1	0	0	0	0
G2	0	4 (40)	2(20)	2 (20)
G3	0	1 (10)	1 (10)	1 (10)
Lymph Invasion +	0	4 (40)	3 (30)	2 (20)
Lymph Invasion -	0	1(10)	0	0
pN0	0	3 (30)	2 (20)	0
pN1	0	0	0	0
pN2	0	2 (20)	1 (10)	0
pN3	0	0	0	2 (20)

the degree of tissue destruction (9-11). *Psychoda albipennis* is an insect species that causes urogenital myiasis in humans. Adult forms of this species belongs to the *Psychodidae* subfamily, and lives especially in humid toilets and domestic bathrooms (10). Flies are attracted to malodor and suppurative lesions where they lay their eggs and develop into larvae. The pathogenicity results from inflammation and toxins secreted by the larvae. The larvae are photophobic, penetrating deep into the tissues with the help of sharp mouth hooks. Genitourinary infestation usually presents as pain and pruritus at the site (8-11). Transmission occurs through the accidental deposit of eggs on oral or genitourinary openings, or by swallowing eggs or larvae that are present on food (9).

The myiasis larvae can develop in two clinical cases: obligate parasites, which thrive on living tissues, and facultative parasites, which attack necrotic tissues and wounds. The larvae generally found in necrotic lesions (cavitary myiasis) are from the genera: *Sarcophaga, Lucilia, Calliphora and Musca*. Genital myiasis can cause unique ulcerated lesions that are often confused with sexually transmitted diseases (12).

The male genital infestation is rare, since the area is usually protected by clothes, and is, therefore less accessible to insect's contact (13-15). In the present series 8 (80%) patients were homeless while 2 (20%) patients lived in support geriatric home. Lyra (16) described a case of a 20-year-old military soldier with furuncular myiasis on penile glans. Two weeks earlier, he had returned from a military mission in a rural area with poor hygiene conditions. The precarious hygiene conditions of such patients justified an adequate environment for myiasis infestation, especially when penile cancer is present, with open wound areas and necrotic tissues.

The etiology of penile cancer has not been fully elucidated. However, its incidence varies according to the practice of circumcision, personal hygiene, presence of phimosis, human papilloma virus infection and tobacco use (4, 5). Despite the level of education varying from illiterate to high-school graduate in the present series, all patients presented with deplorable hygiene conditions at their hospital admission. In this series, all patients were tobacco smokers and only 1 (10%) had been circumcised in adolescence. The remaining 9 (90%) patients presented phimosis.

The 2002 TNM classification for penile cancer, has been criticized by several authors (17-19). Because it is essentially a pathological assessment, it is virtually impossible to clinically determine the precise level of tumor invasion and the real lymph node status. In the study conducted by

Petralia (20), physical examination was able to properly stage the primary tumor in only 8 of 13 patients (61.5%), with overstaging in 2 (15.4%) and understaging in the other 3 (23.1%) patients. Likewise, de Kerviler (21) only obtained a correct clinical staging of penile lesions in 66.6% of patients in their series. In another study conducted by Koifman (5) the authors observed clinical staging accuracy of the primary tumor in 75.2% of 230 patients evaluated.

In the present series we observed clinical staging accuracy of the primary tumor in 50% of cases. When stratifying patients according to the primary tumor, understaging was observed in 25% of patients with T2 and 33.3% of patients with T3, while overstaging took place in 20%, 33.3% and 50%, respectively for T2, T3, and T4 tumors. Misinterpretation of the degree of tumor infiltration of the primary lesion on physical examination could be attributed to local edema, infectious processes that arise at the tumor site and mass effect caused by the presence of the larvae.

The central mechanism responsible for tissue repair after injury is inflammation. Malignant neoplasms use deficiencies in the repair mechanisms to maintain cell growth and proliferation. This double face of inflammation process intended to ensure tissue repair, may undergo changes in their orientation, contributing to the growth and development of neoplasia. The disordered production of inflammation factors by the tumor leads to the blockage of natural apoptosis process (22, 23). In a recent study conducted by Koifman (24) the authors demonstrate through proteomic analysis, the absence of human complement C3 in samples of patients with squamous cell carcinoma of the penis. A possible explanation for these findings lies on the theory that patients with malignancies have a poorer immune response. It is possible that the presence of myiasis in association with penile carcinoma intensify local inflammatory process, creating an ideal environment for tumor proliferation.

The association between myiasis and penile cancer is extremely rare with only 2 reports published in the international literature. Tavares (8) described the first case in the literature. Singh (25) published a case of myasis associated with carcinoma in situ of penile glans.

In the present study, it was possible to observe the process of misinformation among individuals with precarious hygiene habits, leading to the exacerbation of a condition that could have been tackled with a less aggressive treatment, in an initial phase, with proper earlier diagnoses. The association between myiasis and penile carcinoma reinforce the need to implement new awareness campaigns on penile cancer in developing countries.

The occurrence of myiasis in the genitalia area is rare, especially when associated with penile cancer. This condition mainly affects patients with a very low socioeconomic status, characterized by poor hygienic habits. Poorer patients with less education tend to delay longer in seeking medical care and therefore the diagnosis of the disease is frequently performed in advanced stages. To our knowledge this study represents the first series of patients diagnosed with genital myiasis in association with penile carcinoma.

CONCLUSIONS

The occurrence of myiasis in the genitalia is more common in patients with precarious hygienic practices and low socio-economic level. The treatment option varied according to the primary tumor presentation and clinical lymph node status.

CONFLICT OF INTEREST

None declared.

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The percentage of resected and ischemic volume determined by a geometric model is a significant predictor of renal functional change after partial nephrectomy

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ABSTRACT

Purpose: The percentage of parenchyma preserved plays a predominant role in predicting renal function after partial nephrectomy (PN). Currently there is no standard method to estimate preserved renal parenchyma. In this study we propose a formula of the percentage of resected and ischemic volume (PRAIV) determined by a geometric model and evaluate the relationships between renal functional change and PRAIV as well as other clinical parameters.

Materials and Methods: We identified 71 patients who underwent open PN between January 2004 and April 2014. Assuming the kidney to be an ellipsoid with bilaterally equal volume and tumor to be a sphere, we calculated PRAIV by integral calculus. Nadir estimated glomerular filtration rate (eGFR) between postoperative 3 and 12 months were recorded. The correlation between percent eGFR reduction, PRAIV, and other clinical parameters were examined.

Results: On univariate analysis, age (p=0.03), depth of tumor invasion (p=0.004), C index (p=0.003), RAIV (p=0.04), and PRAIV (p<0.001) were correlated with percent reduction of eGFR. However, only age (p=0.007) and PRAIV (p<0.001) were significantly correlated with percent reduction of eGFR on multivariate analysis. Depicting these values along the regression line, we found R^2 was 0.194 and 0.073 for PRAIV and age, respectively.

Conclusions: PRAIV determined by a geometric model is a significant predictor of renal functional change after PN. Using PRAIV, we can estimate percent eGFR reduction preoperatively for better patient consultation and surgical planning.

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INTRODUCTION

Partial nephrectomy (PN) is currently the standard treatment of T1 renal tumors (1-3). Compared with radical nephrectomy, PN provides equivalent oncological control and better preservation of renal function (2). Multiple tumor factors (tumor size and complexity), patient factors (preoperative renal function, presence of a solitary kidney, age, sex, comorbidities), and surgical factors (ischemia type, ischemia duration, amount of preserved renal parenchyma) have been postulated to be associated with renal function after PN (4). Nephrometry systems including C-index, PADUA and RENAL scores were also found to have correlation with surgical complexity and change

in renal function (5, 6). In studies which included the amount of preserved renal parenchyma to access postoperative renal function, the percentage of parenchyma preserved plays a predominant role in predicting renal function (7-9).

Several methods, such as intraoperative visual estimation and analysis of computerized tomography (CT) images, were proposed to estimate the amount of preserved renal parenchyma (7-13). Recently Shin et al. reported a formula using integral calculus to calculate the resected and ischemic volume (RAIV) during PN (14). In their study, RAIV had superior correlation with the absolute and percent change in estimated glomerular filtration rate (eGFR) compared to nephrometry systems including RENAL, PADUA, and C-index. However, the concept of percentage of parenchyma preserved was not included in RAIV. In other words, the same RAIV may cause different changes in patients with various renal parenchymal volumes. In this study we propose a new formula of percentage of RAIV (PRAIV) based on a geometric model. We also compare PRAIV with RAIV, nephrometry systems, and other clinical parameters in predicting the percent reduction of postoperative renal function.

MATERIALS AND METHODS

Under the approval of institutional review board, we identified 71 patients who underwent open PN in a tertiary referral center between January 2004 and April 2014. We retrospectively analyzed their medical records and preoperative abdominopelvic CT or magnetic resonance imaging. Eight patients were excluded for incomplete recording of perioperative parameters. The principal techniques of PN included clamping of hilar vessels until completion of cortex sutures, commence of resection immediately after ice slush applying, and intravenous administration of mannitol as a reno-protective agent.

The cohort of 63 patients had bilateral kidneys. Serum creatinine was measured at a single clinical reference laboratory. Renal function was assessed by estimated glomerular filtration rate (eGFR) using the MDRD2 (Modification of Diet in Renal Disease 2) equation (15). Measurements of renal function were done immediately before operation, and nadir eGFR was recorded between postoperative 3 and 12 months.

In addition to renal function, preoperative demographic information (age, gender, tumor size, depth of invasion) and perioperative parameters (cold ischemia time, estimated blood loss, pathologic report, RENAL, PADUA, C-index, RAIV, PRAIV) were recorded. RAIV was determined by the equation proposed by Shin et al. (14). Assuming the kidney to be an ellipsoid with bilaterally equal volume and tumor to be a sphere, we calculated PRAIV by dividing RAIV with functional renal volume (Figure-1).

Statistical analysis

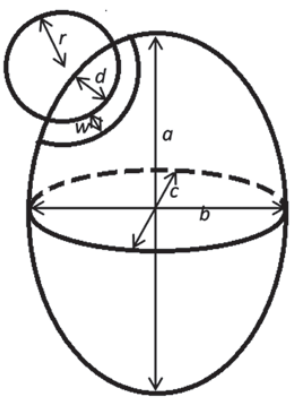
Univariate and multivariate analysis were done to access the relationship between percent reduction of eGFR and demographic and perioperative parameters. The relationships were plotted using simple regression. The coefficient of determination (R^2) indicates how well a regression line fits data. Data analysis was done using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 17.0 for Windows with the null hypothesis rejected at $p<0.05$.

RESULTS

Table 1 lists demographic and perioperative data of the study cohort. Mean age was 57.4 years, and 66.7% of the patients were male. Mean tumor diameter was 3.4cm, and mean depth of tumor invasion was 1.7cm. Renal cell carcinoma was diagnosed in 84.1% of the renal tumors. For the purpose of simplifying calculation of RAIV and PRAIV, the width of peritumor parenchymal resection and ischemization was empirically defined as 0.5 centimeter. Mean RAIV was 12.3cm3, and mean PRAIV was 4.4%. Mean RENAL, PADUA, and C-index were 6.9, 8.2, and 2.4, respectively. As for functional outcome, mean preoperative eGFR was 80mL/min/1.73m^2, and eGFR reduced by a mean of 13.7% postoperatively.

Table-2 shows the correlation between percent reduction of eGFR and clinical parameters. On univariate analysis, age (p=0.03), depth

Figure 1 - Illustration of geometric renal tumor model and calculation process of RAIV and PRAIV.



r = tumor radius
d = depth of invasion
w = width of resection and ischemization
a = height of kidney
b = length of kidney
c = width of kidney

$$\text{RAIV}=\pi\times\int_{r-d}^{r+w}[(r+w)^2-x^2]dx-\pi\times\int_{r-d}^{r}[r^2-x^2]dx=\pi\frac{w[2w^2+3w(r+d)+6rd]}{3}$$

$$\text{Unilateral renal volume (URV)}=\pi\times\frac{a\times b\times c}{6}$$

$$\text{Renal volume replaced by tumor (RVRT)}=\pi\times\int_{r-d}^{r}[r^2-x^2]dx=\pi\, d^2(r-\frac{d}{3})$$

$$\text{Functional renal volume (FRV)}=2\times\text{URV}-\text{RVRT}$$

$$\text{PRAIV}=\frac{RAIV}{FRV}$$

of tumor invasion (p=0.004), C-index (p=0.003), RAIV (p=0.04), and PRAIV (p<0.001) were correlated with percent reduction of eGFR. However, only age (p=0.007) and PRAIV (p<0.001) remained significantly correlated with percent reduction of eGFR on multivariate analysis. Depicting these values along the regression line, we found R^2 was 0.194 and 0.073 for PRAIV and age, respectively (Figure-2). On the other hand, gender, tumor size, cold ischemia time, and preoperative renal function were not significantly associated with percent reduction of eGFR, while RENAL and PADUA had only marginal correlations with renal function change (p=0.05 and 0.07 on univariate analysis).

DISCUSSION

Factors predicting functional change after PN have been an interesting field with many investigations. A strong correlation was found between the quality and quantity of renal parenchyma preserved and long-term renal function (16). Compared with ischemia duration, preoperative renal function, and other perioperative parameters, the percentage of renal parenchyma preserved had an even greater impact on ultimate renal function after PN (7-9). It was reported that a 5% increase in the amount of renal volume preserved carried a 17% reduction of the risk of stage 4 chronic kidney disease (17). In this study we investigated the influence of PRAIV on the functional outcome in a cohort of patients undergoing open PN. We found that PRAIV was the most important predictor of renal functional change.

Various methods in estimating resected renal volume were reported in literature. Theoretically the segmentation algorithm should be the most accurate. However, measuring areas on each axial section of CT scan was time-consuming and required sophisticated software as well as technical expertise in freehand scripting (9, 10, 12, 13). Simmons et al. estimated the percent of functional volume preservation by a cylindrical volume ratio method (7). It only took approximately 5 minutes for each patient but was limited for kidneys with substantial irregular defects. Chan et al. indicated that intraoperative visual assessment of functioning residual renal parenchyma by experienced surgeons who possess an educated cognition was the most accurate predictor of postoperative renal function (11). Tobert et al. compared the accuracy of surgeon assessment of volume preservation to those of 3-dimensional imaging and cylindrical model-based functional volume preservation in

Table 1 - Demographic and perioperative data of 63 patients.

Gender		
No. male (%)	42	(66.7)
No. female (%)	21	(33.3)
Mean age (range)	57.4	(25-83)
Mean cm tumor diameter (range)	3.4	(1-15)
Mean cm depth of tumor invasion (range)	1.7	(0.1-3)
No. pathology results		
pT1a	48	
pT1b	5	
Benign	10	
Mean min cold ischemia time (range)	40.6	(6.6-71)
Mean mL blood loss (range)	330	(50-2100)
Mean RENAL (range)	6.9	(4-12)
Mean PADUA (range)	8.2	(6-13)
Mean C-index (range)	2.4	(0.8-6.7)
Mean cm3 RAIV (range)	12.3	(1.8-45.1)
Mean PRAIV (range)	4.4	(1-16)
Mean mL/min/1.73m^2 eGFR (range)		
Preop	80	(17-137)
Postop nadir	69.3	(12-115)
Mean % eGFR reduction	13.7	(-15-59)

predicting postoperative renal function (18). They found that surgeon assessment of volume preservation was more efficient with accuracy comparable to those of more time intensive alternatives. Nevertheless, visual assessment is subjective in nature and there may be variance among different surgeons.

Shin et al. raised the idea of using a mathematical model to calculate the RAIV and found that RAIV had a good correlation with the absolute and percent change in eGFR (14). For the purpose of better predicting functional outcome, we take into consideration the functional renal volume and propose a new formula to calculate PRAIV. Assuming the tumor as a sphere and bilateral kidneys as symmetrical ellipsoids, we calculate PRAIV using integral calculus. Six parameters, namely, tumor radius, depth of invasion, width of resection/ischemization, height, width, and length of kidney, were required in our formula. According to our study, though both RAIV ($p=0.04$) and PRAIV ($p<0.001$) were correlated with percent reduction of eGFR on univariate analysis, RAIV ($p=0.5$) lost its correlation on multivariate analysis. In other words, lesser PRAIV means more percentage of renal parenchyma preserved with subsequently better postoperative renal function. PRAIV could serve as a more comprehensive and accurate predictor of renal functional change compared with RAIV. The

Table 2 - Univariate and multivariate analysis of factors predicting percent eGFR reduction.

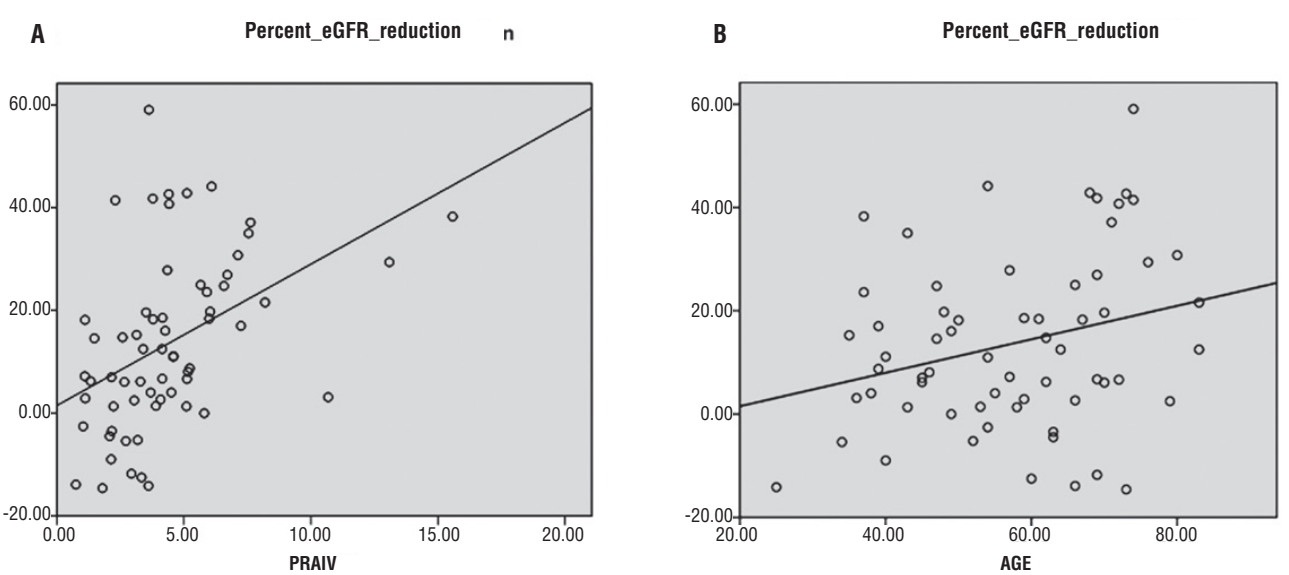
	Univariate		Multivariate	
	Beta	p value	Beta	p value
Gender	0.24	0.06	0.12	0.29
Age	0.27	0.03	0.31	0.007
Tumor size	0.07	0.6	-0.25	0.08
Depth of invasion	0.34	0.004	0.23	0.13
Cold ischemia time	0.12	0.36	0.18	0.1
Preop eGFR	-0.06	0.66	0.11	0.37
RENAL	0.25	0.05	0.13	0.27
PADUA	0.23	0.07	0.13	0.32
C-index	-0.37	0.003	-0.2	0.12
RAIV	0.26	0.04	-0.15	0.5
PRAIV	0.44	<0.001	0.47	<0.001

Beta= standardized coefficient

influence of PRAIV on renal functional change was also greater than that of C-index, while RENAL and PADUA exerted only marginal influence (Table-2). In addition, we found that age, a potential determinant of nephron quality, was correlated with percent reduction of eGFR, though the significance was less than PRAIV (R^2=0.073 and 0.194, respectively).

Yossepowitch reported that cold ischemia time was associated with early postoperative eGFR

Figure 2 - Correlation plots of percent eGFR reduction with PRAIV and age. A, percent eGFR reduction vs. PRAIV, y=1.512 + 2.752x, R^2=0.194. B, percent eGFR reduction vs age, y=-4.958 + 0.324x, R^2=0.073.



changes, but not with eGFR decrease 12 months after surgery (19). Lane et al. also stated that when percentage of parenchyma spared was incorporated into the analysis, duration of ischemia time, either cold or warm ischemia, lost significance in determining ultimate renal function (8). Other studies indicated that when warm ischemia was kept less than 20 to 25 minutes or hypothermia was used, ischemia injury had a less pronounced role in determining renal function (12, 17). In line with the literature, the mean cold ischemia time of our study was 40.6 minute, and it was not a significant predictor of percent reduction of eGFR in the long term.

A major limitation of our study was that the renal tumor model was built geometrically. In fact, the tumor and kidney could hardly be a true sphere and ellipsoid, and the volume of renal cysts and collecting system should be adjusted in estimating functional renal volume. Besides, the calculation process using integral calculus was a little complicated. Nevertheless, our geometric model and formula provided an intuitive concept in estimating PRAIV. More importantly, our results reemphasized the great influence of renal quantity on the functional outcome after PN.

Another challenge to our results is that we arbitrarily defined the width of resection and ischemization as 0.5 centimeter in our series. Frankly speaking, the resection margin may not be identical all around the tumor, and the width of each bite varies suture by suture. Therefore, our results may be biased by inconsistent values of the width of resection and ischemization. Notwithstanding, as long as a histologic tumor - free margin is achieved, it is sufficient to get local tumor control in PN (20). So every effort should be made to render the resection margin as minimal as possible, and intraoperative ultrasound may be used for carefully planning before tumor dissection (21). Besides, the extent of renorrhaphy after tumor excision should be reduced to limit the area of tissue injury.

Other limitations of our study include the small sample size, retrospective nature, and single surgical approach. More validated results could be established if laparoscopic or robot-assisted PN are enrolled. In addition, in our study renal function was accessed using MDRD2 equation. Ideally, for patients with bilateral kidneys split renal function should better be evaluated by renal scintigraphy with technetium-99m-mercaptoacetyltriglycine (22).

CONCLUSIONS

PRAIV determined by a geometric model is a significant predictor of renal functional change after PN. Using PRAIV based mostly on radiographic parameters, we can make a preoperative estimation of percent eGFR reduction for better patient consultation and surgical planning. Additional studies are required to access the applicability of PRAIV in predicting renal functional change after PN of various surgical approaches and in various institutions.

ABBREVIATIONS

PN = partial nephrectomy
CT = computerized tomography
RAIV = resected and ischemic volume
PRAIV = percentage of resected and ischemic volume
eGFR = estimated glomerular filtration rate

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Cystoscopy-assisted laparoscopy for bladder endometriosis: modified light-to-light technique for bladder preservation

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ABSTRACT

Introduction: Endometriosis is a disease with causes still unclear, affecting approximately 15% of women of reproductive age, and in 1%-2% of whom it may involve the urinary tract. The bladder is the organ most frequently affected by endometriosis, observed around 85% of the cases. In such cases, the most effective treatment is partial cystectomy, especially via videolaparoscopy.

Study Objective, Design, Size and Duration: In order to identify and delimit the extent of the intravesical endometriosis lesion, to determine the resection limits, as well as to perform an optimal reconstruction of the organ aiming for its maximum preservation, we performed a cystoscopy simultaneously with the surgery, employing a modified light-to-light technique in 25 consecutive patients, from September 2006 to May 2012.

Setting: Study performed at Campinas Medical Center – Campinas – Sao Paulo – Brazil.

Participants/materials, setting and methods: Patients aged 27 to 47 (average age: 33.4 years) with deep endometriosis with total bladder involvement were selected for the study. The technique used was conventional laparoscopy with a transvaginal uterine manipulator and simultaneous cystoscopy (the light-to-light technique). A partial videolaparoscopic cystectomy was performed with cystoscopy-assisted vesical reconstruction throughout the entire surgical time. The lesions had an average size of 2.75cm (ranging from 1.5 to 5.5cm). The average surgical time was 137.7 minutes, ranging from 110 to 180 minutes.

Main Results: Postoperative follow-up time was 32.4 months (12-78 months), with clinical evaluation and a control cystoscopy performed every six months. No relapse was observed during the follow-up period.

Conclusions: A cystoscopy-assisted partial laparoscopic cystectomy with a modified light-to-light technique is a method that provides adequate identification of the lesion limits, intra or extravesically. It also allows a safe reconstruction of the organ aiming for its maximum preservation.

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Endometriosis; Urinary Bladder; Cystoscopy

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INTRODUCTION

Endometriosis is a gynecologic disease with causes still unclear. It was first described in 1860, but its most accepted etiopathogeny postulating retrograde menstruation was proposed in 1921 (1, 2).

Endometriosis is the presence of stroma and/or endometrial epithelium outside the cavity and the uterine muscles, invading the peritoneum

or embedding on the walls of the pelvic organs (3). It is an estrogen-dependent disorder associated with chronic pelvic pain and infertility (4).

It is estimated that approximately 15% of women of reproductive age are affected by endometriosis (5).

In 1979, the American Fertility Society initially classified endometriosis in 4 stages of severity, but reviewed this classification in 1985 (6, 7). The present classification was introduced in 1997, whereby it stages endometriosis as superficial when it affects the parietal and visceral layers of the peritoneal membrane, and deep when there is more than 5cm penetration of the walls of the organs (8).

The most common sites affected by endometriosis in the pelvic cavity are the torus uterinus, the posterior fornix, the uterosacral ligaments, the rectum, the vagina and the urinary tract (9). However, it may affect other sites, such as the diaphragm, the umbilical cord, the ileum, the lungs, the pleura, the pericardium and the brain (10, 11).

Endometriosis may cause dysmenorrhea, even at the beginning of a woman´s fertile age, dyspareunia, chronic pelvic pain, and peri-menstrual pain (12).

Another frequent disorder is infertility, occurring in up to 60% of the cases.

Specifically, in the urinary tract, there is a 0.3% to 12% incidence of endometriosis; however, it is usually reported as 1%-2% (13), and the most commonly affected sites are the bladder (85%), ureter (9%), kidneys (4%), and the urethra (2%), as shown in Figure 1A below.

When the bladder is affected, 70% of women present pain during urination, dysuria, suprapubic pain and hematuria, especially during the peri-menstrual period.

There is a 20%-35% occurrence of hematuria due to vesical mucous infiltration. Menouria (hematuria during the menstrual period) is infrequent (14).

Urinary tract involvement may be represented by nodules with retractions and/or distortions of the normal anatomy (15), in addition to adherences to the vesico-uterine space.

Partial cystectomy – especially by laparoscopic means - is the most effective treatment for deep endometriosis when the bladder is affected. This surgical procedure is excisional and consists of the removal of the entire bladder wall affected by endometriosis. For this type of procedure, the bladder must ideally present good functional capacity, show a single lesion and be located >5mm of the urethral meatus.

PATIENTS AND METHODS

From September 2006 to May 2012, 25 patients with initial diagnosis of deep endometriosis affecting the bladder wall were treated by the cystoscopy-assisted videolaparoscopic cystectomy with the light-to-light technique (16). (The association of both procedures is meant to identify and delimit the extent of the intravesical endometriotic lesion, to determine the resection limits, as well as to perform an optimal reconstruction of the organ, aiming for its maximum preservation. The patient's average age was 33.4 years, ranging from 27 to 47 years. After clinical assessment and a physical examination with bimanual palpation, the patients were tested for serum urea and creatinine levels, urine (proteinuria or microscopic hematuria) and urine culture, all of which were normal. All patients were submitted to transvaginal ultrasound (TVUS) to diagnose the disease (Figure-1B), and to magnetic resonance (MRI) of the pelvis for surgical planning purposes (Figure--1C). The vesical lesion depicted on MRI is characterized by hyper-signal on T1 and hypo-signal on T2 (17, 18).

Description of the Modified Light-To-Light Technique

The technique we used consisted of conventional laparoscopy, with the patient under general anesthesia and in a horizontal supine (dorsal decubitus) position, with the lower limbs spread out for the cystoscopy procedure. The umbilical scar is punctured with a Veress needle and pneumoperitoneum is performed with CO2 initially up to 20mmHg until introduction of a 10mm umbilical trocar. Upon visibility of the abdominal cavity, the pressure is reduced to up to 12mmHg and 3 trocars are introduced, of which one 10mm trocar

in the umbilical scar, one 10mm trocar in the bisector of the imaginary line going from the anterior superior iliac crest to the umbilical scar on the right, and one 5mm in the exact same position on the left side, as per the representation below.

A videolaparoscopy subsequently performed inventory of the abdominal and pelvic cavity and identified a solid nodular lesion on the vesical dome and vesico-uterine fossa, at times with significant adherence of such organs, as shown in Figure-1D (a).

The procedure above was followed by positioning the transvaginal uterine manipulator and performance of the light-to-light cystoscopy technique, originally described by Seracchioli et al. The endoscopic diagnosis was confirmed by visualization of tissue compatible with endometriosis on the vesical mucous surface. These lesions were blistered purple-blue nodules, containing endovesical material, as shown in Figure1D (b).

The cystoscopy-assisted partial laparoscopic cystectomy with the light-to-light technique

Figure 1A - Endometriosis incidence in utrinary tract

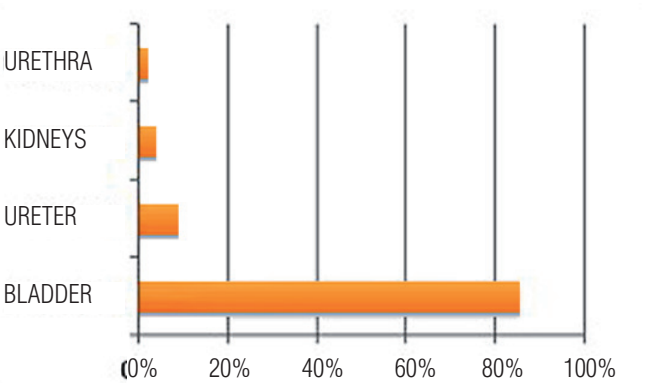


Figure 1B - Transvaginal ultrasound with endometriotic endovesical lesion. (N)

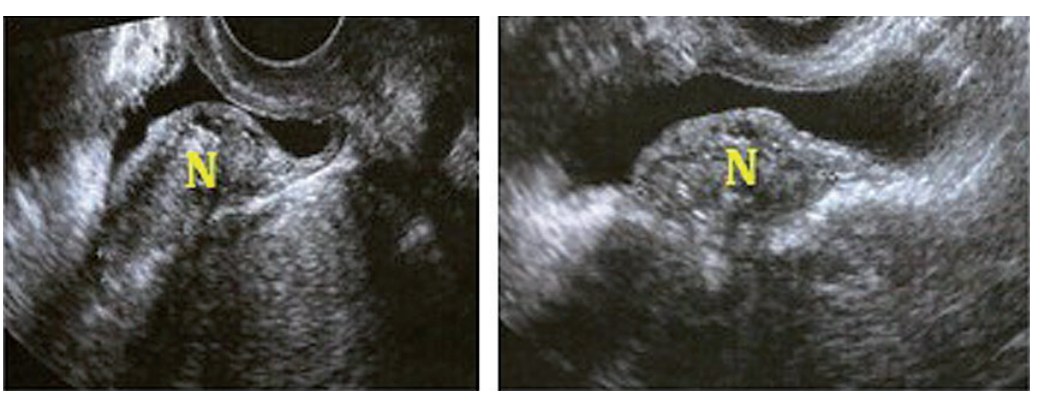


Figure 1C - MRI of the pelvis depicting hypo-signal on T2 (lesion is highlighted).

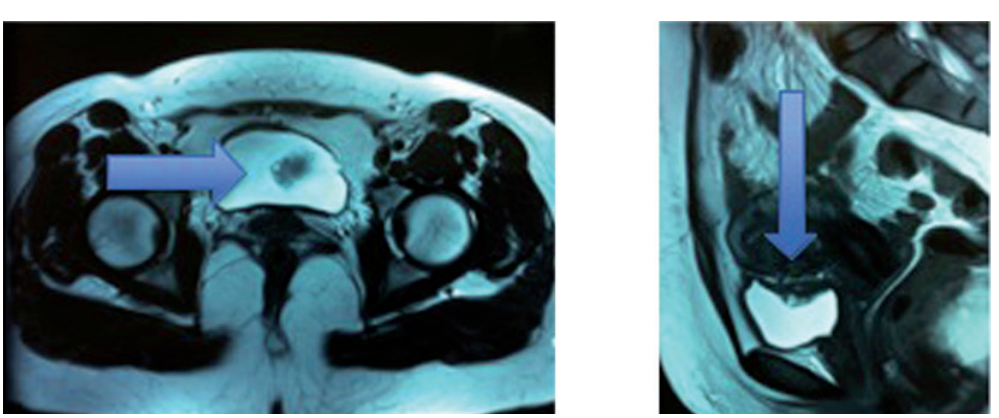


Figure 1D - A - Endometriosis in laparoscopic view, B - Endometriosis in cistoscopic view.

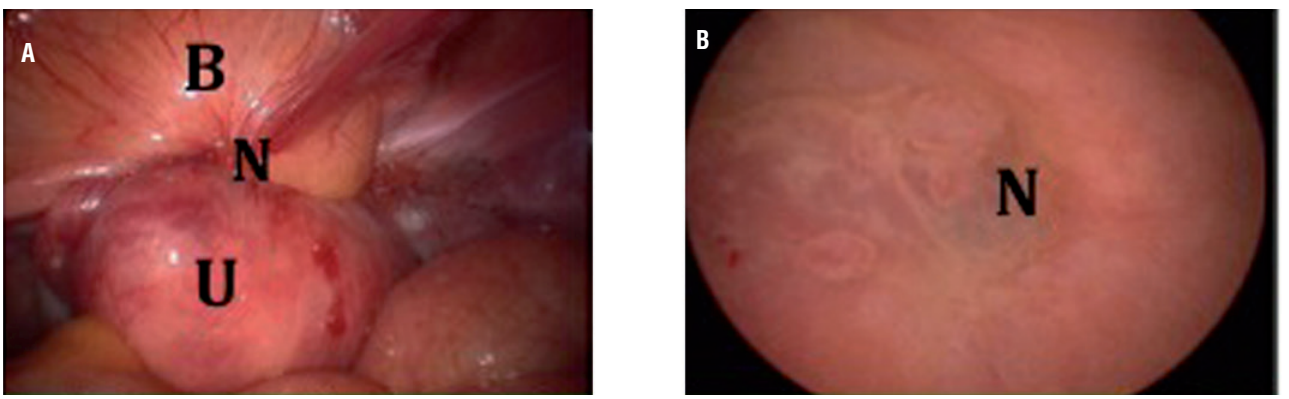


Figure 1D, **(a)** (left): laparoscopic view; (**B**=Bladder, **N**=Node, **U**=Uterus); Figure 1D, **(b)** (right): cystoscopic view; (N=node)

was then performed with some modifications, such as initially not inserting urethral catheters. As the lesions affected the entire bladder wall, a partial cystectomy was performed assisted by cystoscopic visualization throughout the procedure. Both surgeons identified and delimited the lesion, keeping a margin of at least 5mm of healthy tissue. Biopsies of the lower, right lateral, left lateral and superior margins were performed after exeresis of the lesion to eliminate permanence of the disease. The subsequent vesical reconstruction consisted of a one-layer suture with monofilament absorbable 3.0 thread, with continuous cystoscopy monitoring, to ensure better visualization of the suture and final checking of the procedure, thus allowing maximum possible preservation of the healthy vesical tissue (Figure 1E).

All patients maintained a urethral catheter for 7 days.

RESULTS

Of the 25 treated patients, 15 had already undergone previous laparoscopy for treatment of pelvic endometriosis and endometriomas, and 10 had never had any treatment. Surgical time ranged from 110 to 180 minutes, with an average of 137.7 minutes. The resected lesions varied in size, ranging from 1.5 to 5.5cm, with an average of 2.75cm. No significant bleeding was observed and average length of hospital stay was 24 hours.

Follow-up was made every six months by means of clinical assessment and a cystoscopy, with total follow-up time of 32.4 months in average (ranging from 12 to 78 months) (Table-1).

There was no relapse of the disease in all cases. The patients presented normal vesical physiology without alterations in bladder filling or emptying, evidenced by clinical assessment and cystoscopy.

DISCUSSION

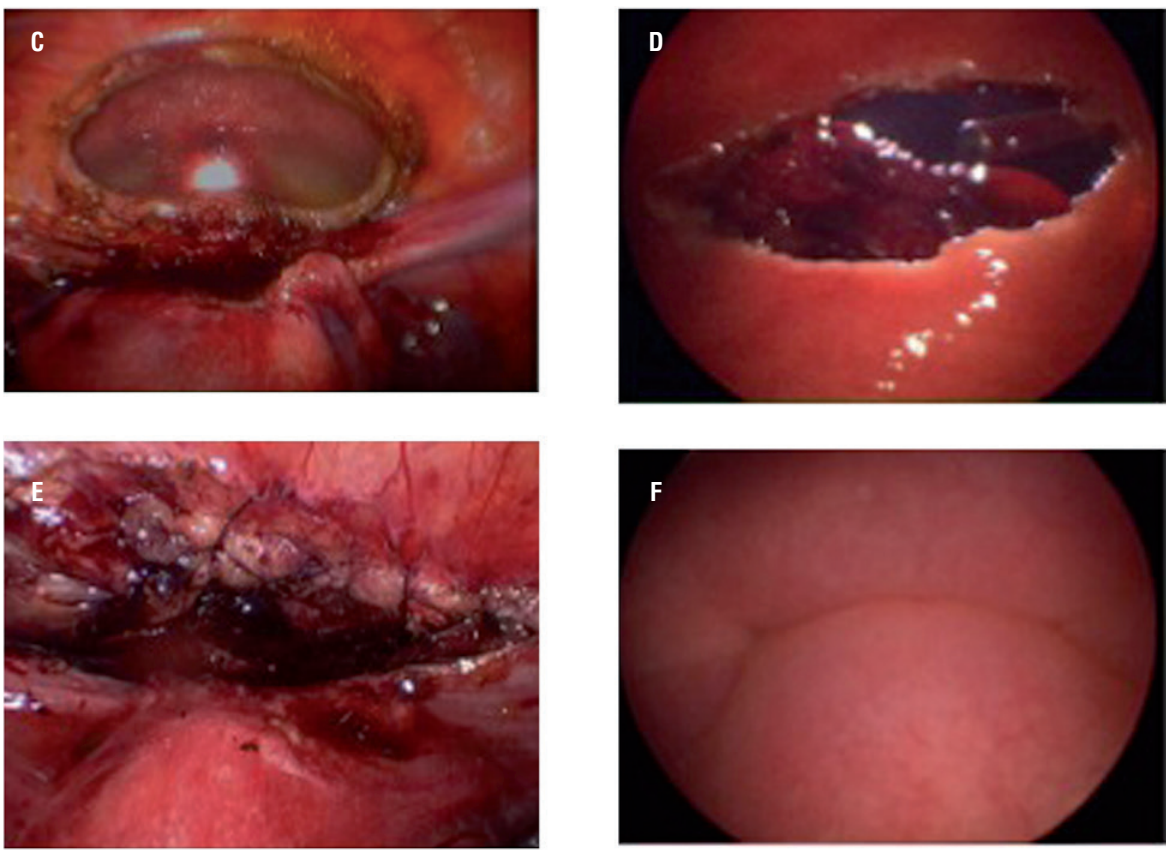
The morpho-physiology of the vesical endometriosis lesions may vary according to the menstrual cycle. However, the lesions are better identified during menstruation. At cystoscopy, these lesions may appear in several colors, such as shades of red, blue, brown or even black. The urothelium is usually rarely ulcerated (19).

Biopsies for differential diagnosis with urothelial carcinoma have been described, but since it rarely invades the mucous, it is difficult to reach a diagnosis by this means.

The differential diagnoses are hyperactive bladder, interstitial cystitis (painful bladder syndrome), urethral syndrome and urothelial carcinoma (20).

In patients with clinical suspicion, diagnosis may be made via a transvaginal ultrasound and, in some cases, by magnetic resonance, as previously described. However, the most effective

Figure 1E - C e E - Endometriosis ressection and suture in laparoscopic view D e F - Endometriosis ressection and suture in cistoscopic view.



Clockwise: **c =** partial cystectomy, laparoscopic view; **d =** partial cystectomy, cystoscopic view; **e =** cystorraphy, laparoscopic view; **f =** cystorraphy, cystoscopic view.

diagnostic method, whether for superficial or deep lesions, is laparoscopy (21).

Treatment of pelvic endometriosis affecting the bladder may depend on several factors, such as age, symptom intensity, fertility, extent of the disease, presence in other organs and level of menstrual dysfunction. As the disease originates outside the bladder (in the peritoneum), subsequently invading it, a vesical transurethral resection is usually an ineffective method (22, 23).

The disease is hormone (estrogen)-dependent, therefore the treatment of superficial lesions is based on hormonal blockade. The most commonly adopted therapy for this purpose is the association of GnRH analogues, progestogens and oral contraceptives (24). This treatment aims at temporarily suppressing endometriosis, reason why it is more recommended for younger patients without deep endometriosis who wish to preserve their fertility. An intrauterine device (IUD) with levonorgestrel may also be used in these more conservative cases, in addition to acting as an adjuvant in corrective surgeries. The IUD importance rests on the fact that is has a duration of up to 5 years and maintains fertility upon discontinuance of its use (25).

There are some options available for cases of deep vesical endometriosis, depending on the extent and site of the lesion in relation to its distance from the urethral meatus.

A transurethral resection with simultaneous use of analogues may be performed. However, the relapse rates in such cases are of approximately 25%-35%, and there are high rates of vesical perforation in diseases of greater extension (26).

Table 1 - Date table.

Patients	Age (Years)	Nodule (CM)	Surgical Time (Minutes)	Follow-UP (Months)
1	30	2.0	180	78
2	27	3.0	180	72
3	28	2.5	172	60
4	33	1.8	175	50
5	29	2.2	168	45
6	42	3.3	150	42
7	42	3.7	155	41
8	36	4.0	160	36
9	36	2.5	120	34
10	29	2.7	120	33
11	33	3.0	132	29
12	31	3.3	128	29
13	34	2.5	124	28
14	47	2.0	120	26
15	33	1.5	110	26
16	30	2.0	122	25
17	32	2.7	128	24
18	33	5.5	150	24
19	29	2.8	127	20
20	28	1.7	118	18
21	30	2.5	120	18
22	35	3.1	115	15
23	38	3.5	126	14
24	39	2.2	111	12
25	32	2.8	122	12
AVERAGE	33.4 years	2.75 cm	137.7 minutes	32.4 months

Therefore, better results are obtained with partial cystectomy in terms of cure of the disease, whether the approach is open, laparoscopic or robotic-assisted (27, 28), with conventional laparoscopic partial cystectomy being the method of choice (27). Several studies report surgical results with 95%-100% symptom remission rates and low rates of relapse (28).

The simultaneous association of cystoscopy with laparoscopy may guide the surgeon in terms of laparoscopic identification of the lesion, with better visibility of the vesico-uterine

space, identification and dissection of the nodule, allowing exeresis of its total extension, and verification of the margins free of the disease.

Healthy 5mm margins of the bladder and a distance of at least 1cm of the urethral meatus should ideally be preserved (29).

The laparoscopic approach has as advantages less blood loss, less time of hospital stay, less use of pain killers and better aesthetic results (30).

We also agree that the interaction between gynecologists and urologists is relevant for the best treatment of this disease and for the performance of successful procedures.

CONCLUSIONS

A cystoscopy-assisted partial laparoscopic cystectomy with a modified light-to-light technique is a method that provides adequate identification of the lesion limits, intra or extravesically. It also allows a safe reconstruction of the organ aiming at its maximum preservation.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Preliminary assessment of neck circumference in benign prostatic hyperplasia in patients with metabolic syndrome

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ABSTRACT

Objectives: To investigate the impact of neck circumference (NC) in the treatment of bening prostatic hyperplasia (BPH) patients with metabolic syndrome (MtS). Additionally, we determined dose response to alpha-blockers and cut-off values for NC and waist circumference (WC), in these patients.

Materials and Methods: Non-randomized, open-labelled, and multi-centre study was conducted between March 2014 and September 2015. The BPH patients were enrolled and were divided into 2 groups: with MtS (Group 1; n=94) and without MtS (Group 2; n=103). Demographic data, anthropometric measurements, blood analyses, uroflowmetric parameters, post voiding residual urine (PVR), prostate volume, quality of life (QoL) index, NC and WC were recorded. Both groups were administered oral alpha-blockers and response to treatment was evaluated. Receiver-operating characteristic (ROC) curves were obtained and significant p was $p<0.05$.

Results: In total, 197 patients were enrolled with mean age of 60.5±8.1 years. Mean NC and WC were higher in MtS patients ($p<0.001$). Uroflowmetry parameters and QoL indexes were comparable between groups before treatment. International prostate symptom score, uroflowmetry parameters, and QoL significant improved in Group 2 than Group 1, at 1st and 6th months of treatment with alpha-blockers. Success rate of treatment was significant higher in Group 2 than Group 1 ($p<0.001$). Cut-off values were 42.5cm and 113.5cm for NC and WC respectively, for response to alpha-blockers in BPH patients with MtS.

Conclusions: MtS can be related with BPH and can negatively affect the response to alpha-blocker treatment. NC can be used for predicting response to alpha-blocker treatment in BPH patients with MtS.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most frequent diseases in aging men (1). Alpha-blockers are the first choice of medical treatment of BPH (2). However, it is still controversial, which patient profile would respond to the alpha-blockers or not (3). Additionally, accurate doses of alpha-blockers are still unknown, in case of comorbidities such as metabolic syndrome

(MtS) (4). Recently, it was established that MtS is one of the causing factors for the development of BPH in aging men (5).

MtS consists of some metabolic risk factors on individuals (6). However, there are several descriptions for MtS, and the criteria of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (ATP III) is the mostly used (7). According to this guideline, the presence of three of the following risk factors constitute MtS: blood pressure (BP) ≥130/85mmHg, fasting blood glucose (FBG) ≥110mg/dL, waist circumference (WC) ≥102cm, High-density lipoprotein (HDL)--cholesterol <40mg/dL, serum triglicerides (TG) ≥150mg/dL, in one individual. Central/visceral obesity is associated with MtS due to visceral adipose tissue (8). According to NCEP, WC is an indicator of central obesity as well as of visceral adipose tissue (7). The measurement of WC sometimes could be very difficult, time consuming, and an inaccurate measurement could be performed in outpatient clinics. Thus, another easy applicable method of measuring visceral obesity is necessary. The neck circumference (NC) comes into question at this point (9). Previous studies showed the usefulness of NC for determining visceral obesity (10, 11). According to our best knowledge, there is no published study on relationship between NC and BPH in patients with MtS.

We here investigate anthropometric details of BPH patients with MtS: NC and WC and additionally, determined cut-off values of NC, WC to predict response to alfa-blocker treatments.

MATERIALS AND METHODS

Study design

This is a prospective, non-randomized, multi-centre, and open-labelled study. Between March 2014 and September 2015, BPH patients who were admitted at family medicine and urology outpatient clinics were evaluated. Our study was approved by instituonal review board. All patients understood aims of the study and also signed consent forms including standards of the 2008 Helsinki declaration and its later amendments or comparable ethical standards. The exclusion criteria were: previous prostate surgery and/or any prostate disease, prostate specific antigen (PSA) >4ng/dL, suspicious prostate nodule in digital rectal examination (DRE), urinary infections, any neurologic disease, allergy to any alpha-blockers, and any bladder disease.

Data collection

247 symptomatic BPH patients were included. All patients were administered non--randomized oral alpha-blockers as tamsulosin 0.4mg, alfuzosin XL 10mg, doxazosin XL 8mg, terazosin 5mg or silodosin 8mg. The exclusion criteria were applied and all patients were divided into 2 groups. Group 1 (n=94) consisted of MtS patients and Group 2 (n=103) was consisted of patients without MtS. Demographic data including age, previous operations, comorbidities were recorded. The international prostate symptom score (IPSS), uroflowmetric parameters, post voiding residual urine volume (PVR), PSA, DRE, prostate volume and quality of life index (QoL) were noted. Anthropometric measurements including NC, WC, height, weight, body mass index (BMI) and blood pressure (BP) were recorded. Supine WC was measured at the level of the umbilicus with the patient breathing silently, and NC was measured with head erect and eyes facing forward, horizontally at the upper line of the laryngeal bulge as in the World Healh Organization guidelines (9). BP including systolic and diastolic was measured twice, with the second measurement taken 10 min. after the first. The means of BP measurements were recorded.

Blood analysis included FBG (mg/dL), TG (mg/dL), low-density lipid (LDL) (mg/dL), and HDL (mg/dL) and total cholesterol (mg/dL). All blood samples were obtained from the largest antecubital vein, after at least 12h of fasting in the morning. According to NCEP criteria the diagnosis of MtS included: BP ≥130/85mmHg, FBG ≥110mg/dL, WC ≥102cm, HDL-cholesterol <40mg/dL, TG ≥150mg/dL.

IPSS, PSA, maximum flow rate (Qmax) in uroflowmetry, and PVR were recorded before treatment as baseline. These parameters were compa-

red in both groups at the 1st month and 6th month of medical treatment. Success rate was accepted when the IPSS decreased at least 4-6 points (12). The cut-off values were determined by using statistical analyses and the receiver-operating characteristic (ROC) curves were drawn. Besides, we evaluated response to alpha-blockers in terms of the cut-off values for NC and WC, in BPH patients with MtS.

Statistical analyzes

The Statistical package for social sciences (SPSS) for Windows ver. 16.0 (SPSS Inc., Chicago, IL) was used for statistical analyzes and all graphs were provided by the same software program. The independent samples t-tests were employed to compare continuous data, and the One-way ANOVA analyzes of variance were also used for comparisons among groups. Statistical analyzes including ROC curves were performed; statistically significant p was accepted as $p<0.05$.

RESULTS

Mean age was 60.5±8.1 years and mean BMI was 31.3±5.7kg/m^2. The demographic data including IPSS, PVR, QoL index, PSA, prostate volume, and antropometric measurements were presented (Table-1). In total, 197 patients (n=94 in Group 1 and n=103 in Group 2) were enrolled into the study. The baseline parameters areshown in Table-2. Age, uroflowmerty parameters and QoL index were comparable between groups except BMI, NC, and WC were significant higher in Group 1 than Group 2 ($p<0.001$).

IPSS, maximum flow rate in uroflowmery (Qmax), PVR, and QoL were significant more developed in Group 2 than Group 1, at the 1st month of oral alpha-blockers administration (respectively; p=0.03, p=0.03, p=0.04, p=0.005). These are presented in Table-3. Similar significance was determined at 6th month of medical treatment (respectively; p=0.02, p=0.03, p=0.04, p=0.001) (Table-4).

Response to alpha-blockers (eloborated according to used drugs) were evaluated at baseline, 1st and 6th months of treatment by using Qmax, IPSS, PVR and QoL index (Table-5). Silodosin was more effective than other drugs in all patients (Table-5). In view of these, alpha-blockers were 80.9% successful in Group 1 (BPH patients with MtS) and 87.4% successful in Group 2 (BPH patients without MtS) ($p<0.001$). In total, success was 84.3% with alpha-blockers. Furthermore, according to statistical analyzes, silodosin was more succesful than other alpha-blockers in terms of developing Qmax, IPSS, PVR, and QoL parameters.

The ROC curves were obtained for determination of the cut-off values in terms of success of medical treatment with alpha-blockers. Mean WC was 113.5cm with 94.4% sensitivity and 42.1% specificity, in patients with metabolic syndrome. The area under the curve was "0.83"; $p<0.001$ (Figure-1A). Mean WC was 91.5cm with 92.3% sensitivity and 52.2% specificity, in Group 2. The area under the curve was "0.86"; $p<0.001$ (Figure--1B). On the other hand, the mean NC was 42.5cm

Table 1 - Baseline demographic data in all patients (n=197).

Parameters	Mean±SD
Age (years)	60.5±8.1
Height (cm)	168.3±7.2
Weight (cm)	88.2±15
Neck circumference (cm)	39.4±4.4
BMI (kg/m^2)	31.3±5.7
Waist circumference (cm)	104.4±14.9
Prostate volume (cc)	42.2±23.5
Triglyceride(mg/dL)	138.8±68.9
High Density Lipoprotein (mg/dL)	49.3±13.1
Systolic BP (mmHg)	116.2±18.7
Diastolic BP (mmHg)	74±13.2
Fasting blood glucose (mg/dL)	99.3±27.4
Qmax	15±4
Qavg	6.1±3
IPSS	23.4±4.1
PSA (ng/dL)	2.6±1.5
PVR (mL)	73.6±40.9
QoL score	3.5±1.6

Abbreviations: **BMI** = Body mass index; **BP** = Blood pressure; **IPSS** = International prostate symptom score; **Qavg** = Mean flow rate in uroflowmetry; **Qmax** = Maximum flow rate in uroflowmetry; **QoL** = Quality of life; **PSA** = Prostate specific antigen; **PVR** = Post voided urine volume

Table 2 - Comparison of baseline parameters in groups.

Parameters	Group 1 (n=94)	Group 2 (n=103)	P Value
Age	59.6±8.3	61.3±7.8	0.14
BMI	35.2±4.4	27.7±4.3	<0.001*
Neck circumference	42.3±3.1	36.7±3.6	<0.001*
Waist circumference	114.2±11	95.4±12.3	<0.001*
Prostate Volume	42.9±22.5	41.5±24.5	0.67
Qmax	14.6±4.2	15.5±3.8	0.12
IPSS	23.4±3.8	23.5±4.8	0.84
PSA	2.7±1.6	2.6±1.5	0.67
PVR	77.3±39.1	70.2±40.3	0.22
QoL score	3.5±1.6	3.5±1.6	0.95

Abbreviations: **BMI** = Body mass index; **IPSS** = International prostate symptom score; **Qmax** = Maximum flow rate in uroflowmetry; **PSA** = Prostate specific antigen; **PVR** = Post voiding residual urine volume; **QoL** = Quality of life score
* Statistical significant P value

Table 3 - Comparison of uroflowmetry parameters and quality of life index between groups one month after treatment with alpha-blockers.

Parameters	Group 1 (n=94)	Group 2 (n=103)	P Value
Qmax	23.1±4	24.4±4.4	0.03*
IPSS	15.2±4.1	14±4.1	0.03*
PVR	66±32.8	56.1±37	0.04*
QoL score	5.1±1.5	5.7±1.5	0.005*

Abbreviations: **IPSS** = International prostate symptom score; **PVR** = Post voiding residual urine; **Qmax** = Maximum flow rate in uroflowmetry; **QoL** = Quality of life score.
*Statistical significant P value

Table 4 - Comparison of uroflowmetry parameters and quality of life index between groups six months after treatment with alpha blockers.

Parameters	Group 1 (n=94)	Group 2 (n=103)	P Value
Qmax	23.1±4.3	24.6±4.9	0.02*
IPSS	15.2±4.1	13.9±4.2	0.03*
PVR	65.4±32.4	55.5±37	0.04*
QoL score	5.3±1.4	6.1±1.5	0.001*

Abbreviations: **IPSS** = International prostate symptom score; **PVR** = Post voiding residual urine; **Qmax** = Maximum flow rate in uroflowmetry; **QoL** = Quality of life score.
* Statistical significant P value.

Table 5 - Comparison of response to treatment according to used alpha-blockers.

Parameters	Silodosin 8mg (n=41)	Tamsulosin 0.4mg (n=39)	Alfuzosin XL 10mg (n=39)	Terazosin 5mg (n=38)	Doksazosin XL 8mg (n=40)	P value
Qmax mL/sec. at baseline	14.9±4.2	15±3.9	15±3.8	15.1±3.6	15.1±3.8	0.9
Qmax at 1st month of treatment	25.9±4.8	24.23.8	23.4±3.5	22.7±4.6	22.5±3.7	0.002*
Qmax at 6th month of treatment	26.4±5.1	24.3±4.5	23.3±3.9	22.6±4.6	22.5±4.2	<0.001*
IPSS at baseline	22.9±4.5	23.7±4.2	23.4±3.6	23.7±4.2	23.5±3.8	0.9
IPSS at 1st month of treatment	11.7±3.8	14±3.4	14.8±3.5	16.1±4.3	16.5±4	<0.001*
IPSS at 6th month of treatment	11.2±3.6	13.9±3.3	15.2±3.5	16±4.4	16.4±4.1	<0.001*
PVR at baseline	76.1±38.7	87.3±39	77.6±34.5	75.8±33.7	77.7±34.8	0.6
PVR at 1st month of treatment	56.8±35.3	67.8±37.6	59.5±35	61.1±34.7	59.1±34.7	0.7
PVR at 6th month of treatment	55.6±35.1	67.7±38.1	58.6±33.9	60.8±33.9	58.6±35.1	0.6
QoL at baseline	3.7±1.5	3.1±1.7	3.7±1.4	3.2±1.7	3.7±1.6	0.1
QoL at 1st month of treatment	6.4±1.3	5.5±1.4	5.3±1.5	4.8±1.5	5±1.6	<0.001*
QoL at 6th month of treatment	6.8±1.2	5.9±1.3	5.5±1.3	5.1±1.4	5.3±1.5	<0.001*

Abbreviations: **IPSS** = International prostate symptom score; **PVR** = Post voiding residual urine volume; **Qmax** = Maximum flow rate in uroflowmetry; **QoL** = Quality of life index.
* Statistical significant P value.
* One way Anova was used to compare values in groups.

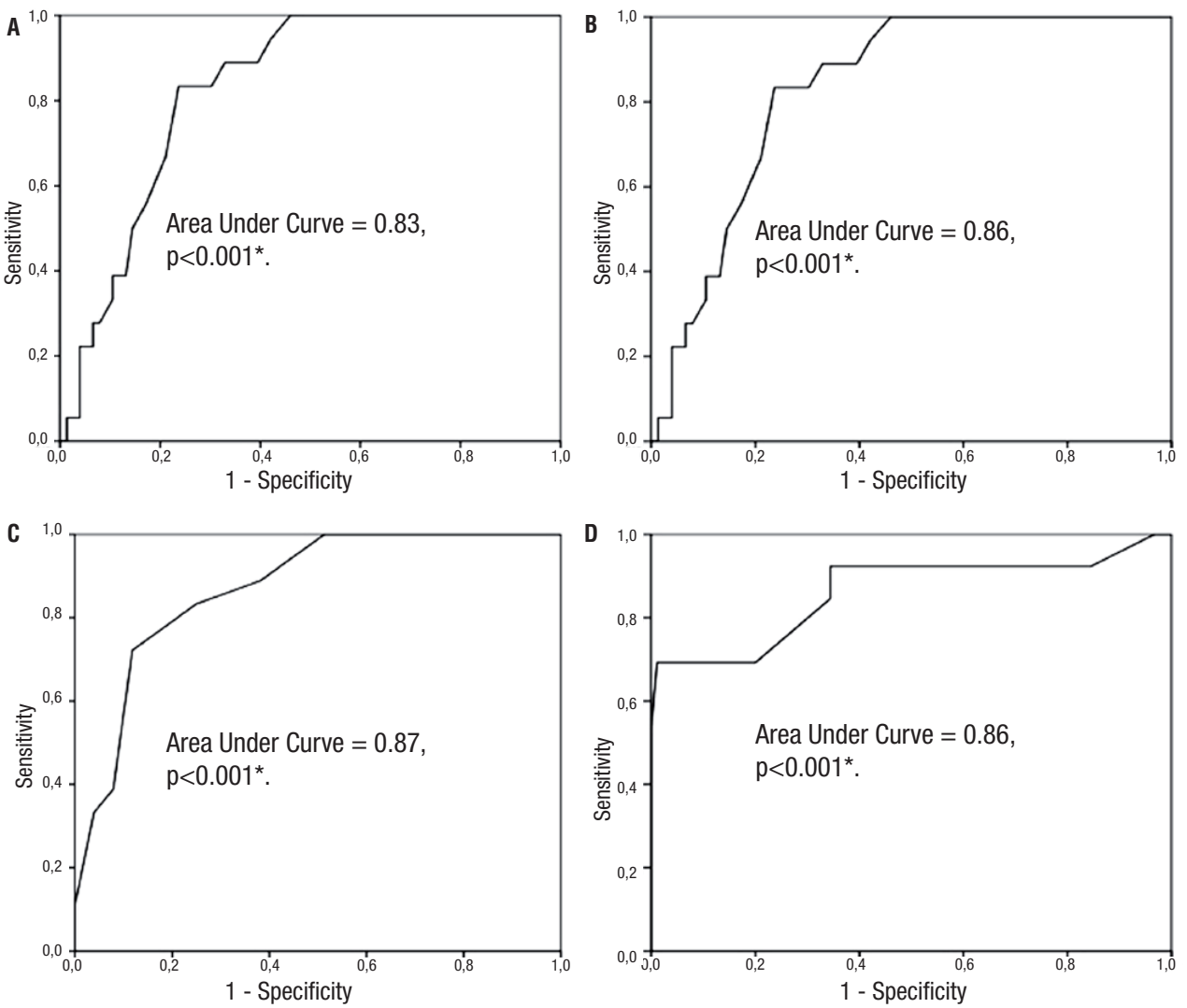
with 88.9% sensitivity and 38.2% specificity, in Group 1 (Figure-1C). The area under the curve was "0.87"; p<0.001. Mean NC was 35.7cm with 92.3% sensitivity and 51.1% specificity, in Group 2. The area under the curve was "0.86"; p<0.001 (Figure--1D). In multivariate analyzes, MtS was considered the determinant factor for accurate response to alpha-blocker treatment. The cut-off value for NC was 42.5cm and for WC was 113.5cm for good response to alpha-blockers.

There was no remarkable side effect in both groups. Dizziness and asthenia were the most common side effects. On the other hand, 7 patients using silodosin and 2 patients using tamsulosin suffered unejaculation. However, all patients carried on medical treatments.

DISCUSSION

MtS is accepted as one of the susceptibility factors for BPH (13, 14). Besides, relationship between BPH and components of MtS including WC was earlier reported (15). The constituve parts of MtS were mentioned above and the WC is one of the essentials among them. WC also depicts visceral obesity. To measure WC sometimes can be very difficult, annoying, and time consuming, notably in the outpatient settings. Thus, NC can

Figure 1 - The cut-off values of neck circumference and waist circumference were drawn with Receiver-operating characteristic curves according to groups. A-The cut-off value for waist circumference in benign prostate hyperplasia patients with metabolic syndrome. B-The cut-off value for waist circumference in benign prostate hyperplasia patients without metabolic syndrome. C-The cut-off value for neck circumference in benign prostate hyperplasia patients with metabolic syndrome. D-The cut-off value for neck circumference in benign prostate hyperplasia patients without metabolic syndrome.



be used in these cases. Recently, NC has been reported as a useful diagnostic tool for determining visceral obesity (9-11, 16). In the present study, we evaluated relationship between NC and BPH, in patients with MtS. Additionally, we showed low response to alpha-blockers in BPH patients with MtS. According to our best knowledge, this is the first study in the published literature on this issue including relationship between NC and BPH.

There were significant developments in IPSS, Qmax, QoL, and PVR with oral alpha-blocker treatments in both groups. However, the development was more significant in Group 2 than Group 1. In multivariate analyses, it was assumed MtS the determinant factor for dose response to alpha--blockers. In subgroup analyzes FDG, WC, and NC (with MtS) were more significant factors for dose response. In ROC curve analyzes, cut-off values

were 113.5cm and 42.5cm for WC and NC, respectively, corresponding to good response to medical treatment in BPH patients with MtS. According to One-way-Anova analyzes, Silodosin was a promising molecule for improving lower urinary tract symptoms in MtS patients in terms of developed Qmax, IPSS, PVR and QoL. Roehrborn and Rosen reported increased QoL index with alfuzosin in BPH patients with MtS (17). Our findings were not parallel to their results. On the other hand, Kupelian et al. reported negative effect of MtS on dose response in BPH (18). Cyrus et al. concluded similar findings (5). Findings of the present study agreed with these studies. In our study, all alfa-blockers were effective but silodosin was more effective than other alpha-blockers. This fact may be associated with more selective effects of Silodosin. Nevertheless, oral alpha-blockers were more effective in Group 2 than Group 1. Additionally, NC was significantly shorter in Group 2 than Group 1. Low response to oral alpha-blockers may be caused by endothelial dysfunction, atherosclerosis-induced pelvic ischemia in MtS patients (19). Moreover, He et al. recently reported role of inflammation in MtS patients with BPH (20). Russo et al. pointed same issue that BPH and MtS were significant associated with high grade of inflammation scores including inversely related to intraprostatic heme oxygenase levels and increased metaflammation (21). However, we focused on clinical effects of alpha-blockers in BPH patients with MtS, more molecular based researches are needed for showing accurate pathway that may be subject of another future study in terms of determing more effective molecules in these patients settings.

DiBello et al. reported BPH and MtS association with elevated PSA levels and these could indirectly connect with decreased odds of having MtS and its components (22). On the other hand, Zoe et al. reported higher PSA levels in BPH patients with MtS (23). Our findings were not in the same line with DiBello et al. (22) but, were similar with results of Zou et al. (23). There was higher PSA levels in Group 1 than in Group 2 without statistical significance. Increased PSA may be caused by multifactorial reasons including inflammation in the first place (24). Demir et al. recently reported apoptosis index and inflammation during alpha-blocker usage (25). Besides, it is now well-known that both BPH and MtS includes inflammation (26). Inflammation associated with BPH and MtS can increase PSA levels. However, Alcaraz et al. reported that these associations may be related with prostate cancer formation (27). Nonetheless, there is need of much more well-designed studies for evidence based results on association between elevated PSA and prostate cancer in MtS patients (27).

There were also some side effects during alpha-blocker usage. Dizzeness was the most common one. However, there were no differences between groups for side effects. Additionally, none of the patients stopped the medical treatment. One of the annoying side effect was unejaculation which most occured with silodosin. This was not a reason to stop treatment.

There are some limitations in our study. Low number of patients in groups is one of them. Because of this, some statistical analyzes should be adequately interpreted: despite significant p values in Table-3 and 4, the differences in all their parameters may really be not clinically significant. At this point, to define exact values of response to treatment may be difficult. Additionally, we did not research the molecular mechanism for relationship between MtS and BPH. The goals of the study were relationship betwen NC and BPH in patients with MtS. Also, the cut-off values for response to contemparary used alpha-blockers were showed, in ROC curves.

Finally, the association between BPH and MtS in terms of measuring WC and NC was presented. We could show that the presence of 43cm or higher NC could be associated with low response to alpha-blocker in BPH patients with MtS. Our results should be verified in future studies with a high number of patients. According to our best knowledge, this is the unique work in the published literature.

CONCLUSIONS

MtS can be related to BPH and can negatively affect response to alphablocker treatment. NC can be used for predicting response to alpha-

-blocker treatment in MtS patients with BPH. NC of at least 43cm and/or above can be associated with low response to alpha-blocker treatment in patients with MtS. Thus, NC is a promising measurement that can show visceral obesity and response to medical treatment in BPH patients with MtS. More well-designed studies with high numbers of patients are needed for more accurate results on this issue.

ABBREVIATIONS

NC = neck circumference
BPH = bening prostatic hyperplasia
MtS = metabolic syndrome
WC = waist circumference
QoL = Quality of Life
ROC = Receiver-operating characteristic

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The burden of chronic ureteral stenting in cervical cancer survivors

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ABSTRACT

Purpose: Ureteral obstruction in cervical cancer occurs in up to 11% of patients, many of whom undergo ureteral stenting. Our aim was to describe the patient burden of chronic ureteral stenting in a population-based cohort by detailing two objectives: (1) the frequency of repeat procedures for ureteral obstruction; and, (2) the frequency of urinary adverse effects (UAEs) (e.g., lower urinary tract symptoms, flank pain).

Materials and Methods: From SEER-Medicare, we identified 202 women who underwent ureteral stent placement prior to or following cervical cancer treatment. The frequency of repeat procedures and rate ratios were compared between treatment modalities. The rates and rate ratios of UAEs were compared between our primary cohort (stent + cervical cancer) and the following groups: no stent + cervical cancer, stent + no cancer, and no stent + no cancer. The "no cancer" group was drawn from the 5% Medicare sample.

Results: 117/202 women (58%) underwent >1 stent procedure. The frequency of additional procedures was significantly higher in patients who received radiation as part of their treatment. UAEs were very common in women with stent + cancer. The rate of UTI was 190 (per 100 person-years), 67 for LUTS, 42 for stones, and 6 for flank pain. These rates were 3-10 fold higher than in the no stent + no cancer control group; rates were also higher than in the no stent + cancer and the stent + no cancer women.

Conclusions: The burden of disease associated with ureteral stents is higher than expected and urologists should be actively involved in stent management, screening for associated symptoms and offering definitive reconstruction when appropriate.

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INTRODUCTION

Ureteral stents are integral to the management of many urologic and non-urologic conditions, however, pain, hematuria, bothersome urinary tract symptoms, infections, and encrustation are still common complications (1-3). While the morbidity of these adverse effects may be acceptable in temporary situations, like following ureteroscopy and lithotripsy, additional considerations are needed to measure the burden in patients requiring long-term stenting. Chronic ureteral stenting may be performed to manage various types of ureteral obstruction in which reconstruction is not feasible or not desired. The need for repeat stent exchanges, often every 3-6 months, and accompanied risk of anesthetic or iatrogenic complications, may cause a significant reduction in overall quality of life (4-6).

Ureteral obstruction in cervical cancer can be the result of disease progression, iatrogenic injury, or treatment toxicity with an incidence as high as 11% (7-10). With current estimates of approximately 245.000 cervical cancer survivors,

there are significant patient and provider implications associated with chronic treatment of ureteral obstruction (11). Using a population-based cohort of women with non-metastatic cervical cancer and ureteral obstruction, we sought to describe the burden of chronic ureteral stenting by detailing two objectives: (1) the frequency of repeat procedures; and, (2) the frequency of urinary adverse effects (UAEs) such as lower urinary tract symptoms or flank pain. In order to estimate the contribution of cervical cancer and its treatment history vs. the contribution of having a ureteral stent on the frequency of UAEs we created several comparison groups. We compared the frequency of UAEs in women with cervical cancer and a stent to women with cervical cancer and no stent; we also compared the event rates to women without cancer who did or did not have a stent.

MATERIALS AND METHODS

Study Population

We have previously described how using the linked SEER-Medicare database we created a cohort of 1.808 women >66 years of age with non-metastatic cervical cancer diagnosed between 1992-2007 (10). Non-cancer controls were matched to cases 3:1 on birth year and race. These 5.424 controls were drawn from the 5% sample of Medicare beneficiaries residing in SEER areas with complete claims data and no history of pelvic malignancy.

From SEER, we obtained cancer subject's basic demographic information including age at cancer diagnosis, race and ethnicity. Comorbidities were assessed by calculating the Charlson index from Medicare claims in the 12-months period before cancer diagnosis (12). Cervical cancer stage was determined based on the International Federation of Gynecology and Obstetrics (FIGO) staging system using the extension code and lymph node status from SEER. We identified primary cancer treatment as treatment received in the first 12 months after cancer diagnosis. Women were divided into 1 of 3 non-overlapping treatment groups: 1) External beam radiotherapy and brachytherapy (EBRT + BT), 2) Radiotherapy and surgery (RT + surgery), and 3) Surgery alone, to determine if specific treatment modalities were risk factors for requiring additional stent procedures. Patients were followed from the start of their cancer treatment to death or end of study period (Dec 31, 2009).

OUTCOMES

Primary objective

From the base cohort of 1808 women, we selected those who underwent at least one ureteral stent procedure in the 12 months prior to or at any time after cervical cancer treatment. All subsequent stent procedures were tallied as separate events. Ureteral stent procedures included stent placement, stent removal and, less commonly, nephrostomy tube placement and were identified using the respective ICD-9 procedure codes and CPT codes from MedPAR Inpatient, NCH and Outpatient Medicare claims data (see appendix). To avoid double counting, we required at least seven days between stent procedures. We described the demographic and clinical characteristics of the stented vs. non-stented cervical cancer cohort; comparisons were made using Student's t-test or chi-square test, as appropriate.

We constructed a histogram of the total number of stent procedures performed per woman between the first procedure and end of the study period or death. Among cases who underwent stent removal, we separately described the frequency of nephrostomy placement. We did not assess the rate of stent change among the controls. We then accounted for differences in follow-up time by calculating the rate of stent procedures and compared rates and rate ratios across different cervical cancer treatment groups (EBRT + BT, Surgery + RT and Surgery). Poisson regression was performed to obtain multivariable-adjusted rate ratios, balanced for differences in demographic and clinical characteristics across treatment groups.

Secondary objective

UAEs, as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events were defined by a Medicare claim with an ICD-9 code corresponding to lower urinary tract symptoms, hematuria, incontinence,

urinary retention, renal colic, urinary stones, or urinary tract infections (see appendix). We compared the rates of UAEs in our cohort of cancer cases with a stent (stent + cancer; n=202) to women with cancer but no stent (no stent + cancer; n=1606), controls with a stent (stent + no cancer; n=79), and controls without a stent (no stent + no cancer; n=5345). For women with a stent, UAEs were recorded from the time of initial stent placement in both the cancer cases (stent + cancer) and controls (stent + no cancer). In non-stented women, UAEs were recorded using a pseudo-diagnosis date based on FIGO stage in cases (no stent + cancer) and age-matching in controls (no stent + no cancer). UAEs were recorded from the initial time point through the end of study period or death. Specific UAEs were considered independently and each event could be counted more than once; however, to avoid double counting we required at least 7 days between claims for the same UAE. Rates of UAEs and multivariable-adjusted rate ratios are reported across the 4 groups, using Poisson regression. All statistical analyses were performed using SAS v9.3 (SAS Institute).

RESULTS

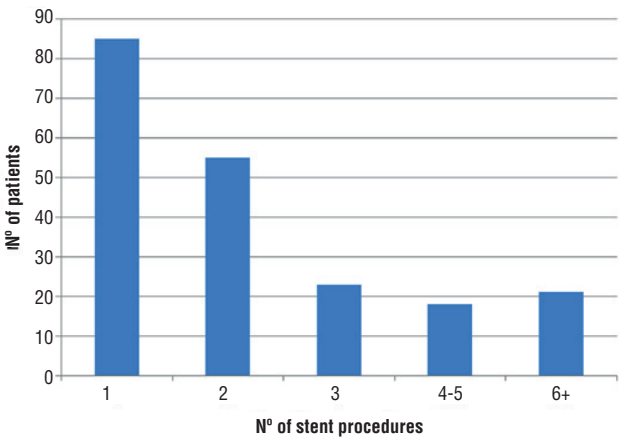
From our initial population of 1808 women, we identified 202 (11.2%) who underwent at least one ureteral stent procedure in the 12 months prior to or any time after cervical cancer treatment. Among these 202 women (stent + cancer), there were a total of 540 stent procedures performed over 472 person-years. Primary cancer treatment was as follows: 117 were treated with EBRT + BT, 50 with Surgery + RT, and 35 with Surgery. The mean age was 73.7 years and was similar across treatment groups. Median follow-up was 2.5 years in the stent + cancer cohort compared to 4.3 years in the no stent + cancer group (p<0.0001). Advanced disease (FIGO stage III or IV) and death as endpoint were significantly more common in the stent + cancer patients compared to the no stent + cancer group (Table-1).

Of the 202 women, 85 (42%) underwent one stent placement procedure (no re-treatments), 55 (27%) were treated twice, and the remaining 62 (31%) were treated 3 or more times (Figure-1). 51 (25%) had the initial stent procedure in the 12

Table 1 - Demographic and clinical characteristics of women with cervical cancer by ureteral stent.

	Stent + Cancer	No Stent + Cancer	p-value
No. of patients, n	202	1606	
Age at cancer diagnosis, mean (SD)	73.70 (5.64)	74.77 (6.35)	0.01
Charlson Score, n (%)			
0	137 (67.8%)	1009 (62.8%)	0.16
≥ 1	65 (32.2%)	597 (37.2%)	
FIGO Stage, n (%)			
1	51 (25.3%)	883 (55.0%)	
2	58 (28.7%)	451 (28.1%)	<0.0001
3-4 or Unknown	93 (46.0%)	272 (16.9%)	
Follow-up in years, Median (range, SD)	2.5 (0.04 to 16.2, 3.2)	4.3 (0.01 to 17.9, 4.0)	<0.0001
Death as endpoint, n (%)	154 (76.2%)	961 (59.8%)	<0.0001
Treatment type, n (%)			
EBRT + BT	117 (57.9%)	675 (42.0%)	
RT + Surgery	50 (24.8%)	372 (23.2%)	<0.0001
Surgery	35 (17.3%)	559 (34.8%)	

Figure 1 - Number of stent procedures (initial and subsequent) performed in women with cervical cancer.



months prior to cancer treatment, 91 (45%) in the 12 months after treatment (including on the actual day of treatment), and 60 (30%) had the initial stent procedure more than 12 months after treatment. The most common initial procedure was cystoscopy with stent placement (57%, CPT 52332) followed by nephroureteral stent placement via percutaneous approach (20%, CPT 50393). Similar frequencies were observed for subsequent procedures as well. Stent removal without simultaneous replacement was performed in 80 patients, <11% of whom subsequently had a nephrostomy tube placed.

The rate of stent procedures was highest (1.54 per person-year) in the EBRT + BT group, followed by the Surgery + RT group (1.00 per person-year) and Surgery group (0.56 per person-year). After adjustment for age, race, FIGO stage and Charlson score, the RR was 2.40 (95% CI: 1.69-3.41) for EBRT + BT group and 1.81 (95% CI: 1.26-2.59) for Surgery + RT group, compared to Surgery group (Table-2).

The rate (events/100 person-years) was determined for specific UAEs including lower urinary tract symptoms (LUTS), hematuria, incontinence, urinary retention, renal colic, urinary stones, or urinary tract infections (including pyelonephritis) and compared between groups (Table-3). The observed rate of UAEs in patients with stent + cancer was highest for UTIs (190), LUTS (67), and stones (42). The adjusted rate ratio (RR) was significantly higher in the stent + cancer group for all UAEs when compared to the no-stent + cancer group. With the exception of urinary stones, adjusted RRs were also higher in the stent + cancer group vs. the stent + no-cancer group, however, to a lesser extent (Table-4).

DISCUSSION

Quantifying the burden of chronic ureteral stenting is important to improve the quality of life of cancer survivors. This is particularly important in cervical cancer because ureteral obstruction occurs in 11%. We show that over 50% of the women who had a ureteral stent placed underwent an additional stent procedure, and over 30% underwent 3 or more procedures. We also show that the incidence of UAEs in women who underwent stent placement was significantly higher than cervical cancer patients without stents as well as control patients with stents.

Ureteral stenting in patients with cervical cancer may be necessary for disease progression (i.e., malignant ureteral obstruction) or for ureteral stricture occurring as an adverse effect of

Table 2 - Rate and risk of stent procedures among the cervical cancer cases who underwent ureteral stent placement

	EBRT+BT	Surgery+RT	Surgery
No. of patients	117	50	35
No. of person-years	227.20	122.54	122.26
Unadjusted Rate* (95% CI)	1.54 (1.39-1.71)	1.00 (0.83-1.19)	0.56 (0.44-0.71)
Unadjusted RR* (95% CI)	2.77 (2.14-3.59)	1.79 (1.33-2.41)	1.00
Adjusted RR* (95% CI)	2.40 (1.69-3.41)	1.81 (1.26-2.59)	1.00

* Rates and rate ratios were obtained from Poisson regression. Adjusted rate ratios were further adjusted for age (65-69, 70-74, 75-79, 80-84, 85+), race (white, black, Hispanic, Asian, other/unknown), FIGO stage (1, 2, 3, 4, unknown), and Charlson comorbidity score (0, 1, 2+).

Table 3 - Rate and risk of UAE among cervical cancer cases and controls.

	Controls (n=5424)		Cases (n=1808)	
	No cancer + no stent	No cancer + stent	Cancer + no stent	Cancer + stent
No. of patients	5,345	79	1606	202
No. of person-years	45,917.90	701.11	7360.89	472.00
Unadjusted Rate* (per 100 person-year)				
Lower Urinary Tract Symptoms	17.9	36.5	24.7	67.2
Hematuria	1.24	4.43	2.67	7.42
Incontinence	6.73	21.99	8.41	20.97
Retention	0.95	1.95	0.73	7.84
Renal Colic/Flank pain	0.58	3.90	0.65	5.93
Stones	1.75	88.67	1.54	41.53
UTI/Pyelonephritis	51.02	113.15	58.36	190.48
Adjusted RR† (95% CI)				
Cystitis and Spasm	1.00	1.86 (1.62-2.14)	1.37 (1.29-1.44)	3.80 (3.40-4.27)
Hematuria	1.00	3.13 (2.08-4.71)	2.12 (1.79-2.52)	5.87 (4.15-8.30)
Incontinence	1.00	2.84 (2.37-3.42)	1.23 (1.12-1.34)	3.17 (2.59-3.88)
Retention	1.00	1.99 (1.08-3.65)	0.76 (0.57-1.01)	8.48 (6.02-11.94)
Renal Colic/Flank pain	1.00	6.02 (3.82-9.49)	1.07 (0.78-1.48)	10.22 (6.85-15.24)
Stones	1.00	48.14 (42.38-54.68)	0.85 (0.70-1.05)	24.57 (20.86-28.94)
UTI/Pyelonephritis	1.00	1.80 (1.66-1.95)	1.12 (1.08-1.16)	3.75 (3.50-4.01)

cancer treatment. While malignant obstruction is associated with a median survival of only 3-6 months, ureteral stricture often becomes a chronic medical problem throughout the cancer survivorship phase (13, 14). Because of complexities in the multi-disciplinary management of patients with non-urologic malignancies, urologists may be removed from ureteral obstruction management decisions; in some centers the gynecologic oncologist may consult interventional radiology instead. Our findings support the conclusion that urologists should be actively involved in the management of these patients to manage stent-related side effects, monitor for stent failure or decline in renal function, and offer definitive reconstruction when indicated.

The morbidity related to ureteral stents has been well described. Possible complications include pain, voiding symptoms, bleeding, infections, encrustation, and the potential to be forgotten (15, 16). Because of the proximity of the cervix to the bladder and other urologic structures, treatment of cervical cancer is associated with many urinary side effects irrespective of stenting (17, 18). We hypothesized that patients with both cervical cancer and a ureteral stent would have higher rates of UAEs than each group separately; however, the rate ratios were more extreme than we expected. The only UAE that was not more common in the stent + cancer group was urinary stones; this was most common in the stent + no cancer group where calculi (renal or ureteral) was the indication for stent placement in over 50% of the patients.

Some limitations of our study deserve mention. First, we cannot know the exact reason why a stent was placed. There was significant variation in the timing of stent placement and treatment, suggesting differences in the etiology of ureteral

Table 4 - Rate ratios of UAE among cervical cancer cases and controls.

	Controls (n=5424)		Cases (n=1808)	
	Controls without stent	Controls with stent	Cases without stent	Cases with stent
Adjusted RR* (95% CI)				
Cystitis and Spasm	-	1.00	-	2.05 (1.72-2.45)
Hematuria	-	1.00	-	1.88 (1.12-3.14)
Incontinence	-	1.00	-	1.11 (0.85-1.45)
Retention	-	1.00	-	4.26 (2.16-8.39)
Renal Colic/Flank pain	-	1.00	-	1.70 (0.96-2.99)
Stones	-	1.00	-	0.51 (0.43-0.61)
UTI/Pyelonephritis	-	1.00	-	2.08 (1.88-2.30)
Adjusted RR* (95% CI)				
Cystitis and Spasm	-	-	1.00	2.79 (2.48-3.14)
Hematuria	-	-	1.00	2.76 (1.93-3.96)
Incontinence	-	-	1.00	2.58 (2.09-3.19)
Retention	-	-	1.00	11.21 (7.37-17.04)
Renal Colic/Flank pain	-	-	1.00	9.53 (5.97-15.21)
Stones	-	-	1.00	28.76 (22.82-36.25)
UTI/Pyelonephritis	-	-	1.00	3.35 (3.12-3.60)

* Adjusted rate ratios were obtained from Poisson regression, with further adjustment for age (65-69, 70-74, 75-79, 80-84, 85+), race (white, black, Hispanic, Asian, other/unknown), and Charlson comorbidity score (0, 1, 2+).

obstruction and the likelihood of resolution. Still, by excluding women with metastatic disease and limiting our analysis to those with a diagnosis of ureteral obstruction or ureteral stricture, we have shown that there is a sensitivity of 100% and specificity of 99% for detecting ureteral strictures after cervical cancer treatment (19). Second, we don't know if a stent was placed on a different side or in conjunction with a minimally invasive procedure to treat the obstruction. We did observe that very few patients received definitive reconstruction (less than 5%); better integration of urologists in the management of these women may help get them access to reconstructive options. Third, we cannot know whether the stent was the cause of the UAEs, only that stent placement was highly associated with ureteral stenting. Because stenting was so highly correlated with advanced stage cancer and treatment with radiotherapy, we could not isolate the effect of the stent from these other factors in multivariate models. Finally, the patient characteristics and outcomes observed in this Medicare population may differ from the experience in other groups of cervical cancer patients.

CONCLUSIONS

Ureteral stents may represent the only long-term treatment option for certain patients with ureteral obstruction. Furthermore, the degree of urinary adverse effects in patients with ureteral stents may vary considerably between different populations. In our study, women with ureteral stents treated for cervical cancer had significantly higher rates of UAEs compared to patients with ureteral stents without cancer. Because of the complexity involved in stent management, including coordination of exchanges, assessment of adverse effects, and continual consideration for definitive

reconstruction, urologists should remain actively involved in the care of such patients.

ABBREVIATIONS

UAEs = urinary adverse effects
LUTS = Lower urinary tract symptoms
EBRT + BT = External beam radiotherapy and brachytherapy
RT + Surgery = Radiotherapy and surgery
FIGO = International Federation of Gynecology and Obstetrics
RR = Rate ratio

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CONFLICT OF INTEREST

None declared.

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Cystometric analysis of the transplanted bladder

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ABSTRACT

Objective: Cystometric evaluation of the bladder after autotransplant and isogeneic transplant in female rats.
Material and Methods: Two groups were constituted: (A) bladder autotransplant with two subgroups: R1 – (control) and R2 – (bladder transplant); (B) isogeneic bladder transplant with three subgroups; T1 – (control); T2–T3, two subgroups observed for 30 and 60 days after transplant, respectively. All animals underwent cystometric evaluation. Afterwards, the bladders were removed for histological study.
Results: The transplanted bladders did not show significant changes in filling/storage and emptying/micturition functions after 30 and 60 days of evolution. Upon macroscopical evaluation, there was good revascularization and the tissue was well preserved.
Cystometry results: Did not show significant differences in the micturition pressure in subgroups T2-T3, but did between subgroups R1–R2, T1–T2, and T1–T3. Significant differences were verified in the micturition interval between T1–T3, T2–T3, but not between R1–R2, T1–T2. There was significant difference in the micturition duration between T1–T3 but not between R1–R2, T1–T2 and T2–T3. No fistula was noted on the suture site nor leakage of urine in the abdominal cavity or signs of necrosis or retraction were observed.
Conclusions: Transplant of the bladder was shown to be a viable procedure. The results indicate that there was structural and functional regeneration of transplanted bladders, and these results indicate that it is possible that vascular endothelium growth and neurogenesis factors are involved and activated in the process of the preservation or survival of the transplanted organ.

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INTRODUCTION

A considerable number of patients requires augmentation or reconstructive cystoplasty to improve bladder urine storage and continence as well as to provide protection of the upper urinary tract. Diverse segments of the gastrointestinal tract, including gastric, small intestine and colon segments, have been employed for this aim (1-5). Alternative natural tissues taken from the uterus, peritoneum, lyophilized dura, pericardium and placenta have also been utilized for cystoplasty (6-12). Furthermore, synthetic materials such as Teflon, sylastic, polyvinyl sponges, poly-alpha amino or collagen/polyglactin membranes have also been tried (13-18). However, all these procedures are associated with many complications including metabolic and electrolyte disturbances, lithiasis, infections, neo-bladder spontaneous rupture or perforation and neoplasia (1-5). To avoid such complications, the use of living partial bladder transplantation has recently been proposed as an alternative procedure for bladder augmentation (5, 19, 20). Although this procedure was

successful in increasing bladder capacity and long term survival of the transplants, it consisted of a two stage intervention and used only the cranial third of the donor bladder. It become of interest to determine whether a similar procedure using the whole supratrigonal bladder for transplantation and performed in a single operation was feasible. Furthermore, a more objective evaluation using a continuous cystometrogram of the transplanted bladder function was deemed necessary.

Consequently, the main objective of the present study was to examine the feasibility of supratrigonal bladder transplantation using autologous and syngeneic transplants. Once the feasibility of the procedure was documented a second objective was proposed to determine whether the transplanted bladders exhibit normal functions using cystometry.

MATERIALS AND METHODS

Experiments were conducted using 45-50 days old Wistar and spontaneous hypertensive female rats (SHR). Wistar rats were employed for the partial bladder autotransplantation whereas SHR were used for the syngeneic transplant experiments. All the procedures followed recommendations of the Committee of Ethics in Animal Experimentation of the Ribeirão Preto Medical School–USP.

Supratrigonal bladder transplant experiments were initially performed to determine the feasibility of the surgical procedure. Female Wistar rats were anesthetized with tribromoethanol 2.5% (1mL/100g body weight), supplemented with additional doses as required. A low median laparotomy was performed to expose the urinary bladder; the supratrigonal segment of the bladder was excised avoiding any damage to the ureter entrances and placed immediately in a container with ice-cold NaCl solution (0.9g/100mL). After 30 min in this solution the excised supratrigonal bladder segment was sutured to the bladder base using continuous 7.0 polyglycolic acid sutures in both anterior and posterior faces leaving both ends of the sutures free. The free endings of both sutures were used to fix the omentum to the anterior and posterior faces of the reconstituted bladder. The abdominal wall incision was closed in two layers using 6.0 polypropylene monofilament. A PE-50 catheter was introduced into the reconstituted bladder through the urethra to allow urine drainage during the post-operative period. This catheter was fixed to the external urethral meatus with a 7.0 polyethylene suture and removed three days later under ether anesthesia. All animals received intrarectal acetaminophen (20mg/kg) after the surgical procedures. No immunosuppressive drugs were used. Once the feasibility of the surgical procedure was established syngeneic transplantation experiments were performed in SHR using a similar procedure.

After the surgical procedures, autotransplanted and syngeneic transplanted rats as well as age-paired control non-operated rats were kept under similar housing conditions (temperature 22 ± 2^{o}C and 12:12h light/dark cycle) with free access to food and water.

Continuous cystometrogram experiments

Thirty days after bladder autotransplantation or 30 and 60 days after syngeneic bladder transplantation both control and operated animals were weighed and anesthetized with urethane (1.2g/kg, subcutaneously). They were placed in a dorsal recumbent position and an incision was made on the anterior abdominal wall (for the operated rats, in the same site of the previous surgery) to expose the bladder (non-operated animals) or the reconstituted bladder (transplanted rats); one end of a PE-50 catheter, containing a small collar created by heating, was introduced into the bladder through a small incision in the bladder dome (including the omentum in the transplanted rats) and tied firmly to the bladder with a silk ligature. The other end of the catheter was linked via a T--connector to a pressure transducer (BLPR2, World Precision Instruments Inc, Sarasota, FL, USA) to record intravesical pressure and to a micro-infusion pump (Model 780.200, KD Scientific Inc. Holliston, MA, USA); warm saline was infused continuously at a rate of 0.08mL/min. Intravesical pressure data was recorded, stored and analyzed using the Windaq software (Dataq Instrument Inc. Akron OH, USA). The following cystometrogram parameters were measured: a) maximal micturi-

tion pressure (peak intravesical pressure developed during micturition contractions), b) micturition interval (time interval between the return of intravesical pressure [IVP] to baseline after a micturition contraction and the beginning of the next micturition contraction, i.e., time point at which the IVP showed a rapid increase), c) duration of micturition contractions, time lapsed from the beginning of the micturition contraction (see above) up to the return to baseline of the IVP.

Histology

After finishing the cystometrogram experiments the animals received an overdose of urethane i.p. The chest was opened to expose the heart and a cannula was inserted into the left ventricle and pushed up into the ascending aorta; an incision was also made in the right auricle to allow drainage and an intracardiac perfusion using cold saline (300mL) followed by buffered 4% paraformaldehyde (300mL) was performed. The whole bladder was then excised, immersed in the same fixative and kept at 4°C until further processing. Bladders were embedded in paraffin and 10µm sections were mounted on microscopic slides and stained with hematoxylin-eosin or Masson's trichrome stain. Slides were observed in an optical microscope and pictures were taken with a Microscopic Axiophot and Axiovision 4.8.1, Carl Zeiss Germany.

Statistics

Body weight, maximal intravesical pressure, micturition interval and micturition duration values are expressed as mean±SEM. Statistical significance of differences between mean values of these parameters for control and autotransplanted rats was determined using the Student's t-test. Statistical significance of differences between mean values of these parameters for control and 30 and 60 days for syngeneic transplanted rats was determined using Analysis of Variance (ANOVA) followed by the Bonferroni test to identify differences among the subgroups. A value of $P<0.05$ was considered statistically significant. Statistical analysis and graphs were done using the GraphPad Prism Program (GraphPad Prism 5.01, San Diego, CA, USA).

RESULTS

Post-operative follow-up

Out of ten autotransplanted rats two showed local infection and dehiscence of the abdominal wall suture three days after surgery and were excluded from the study. The eight remaining animals (80%) which survived the 30 day period exhibited a mean body increase of 35g without showing any complications. After the CMG determinations the omentum was removed from the bladder and no tissue discoloration, micro-abscesses, suture leakage or strictures were observed, and the sutures were entirely reabsorbed. Three animals had a single, friable calculus which did not adhere to the bladder wall or to the surgical site. The cystometrogram (CMG) data from these animals were not included in the quantitative analysis. Of 19 syngeneic transplanted rats two died within 24 hours after surgery; the remaining animals survived for 30 and 60 days uneventfully. Mean weight gain was 34g and 51g for the 30 day and 60 day transplanted rats, respectively. After the CMG determinations the omentum was removed from the bladder and similarly to the autotransplanted rats no tissue discoloration, micro-abscesses or strictures were observed. Intriguingly, no intravesical calculi were observed in these animals. In addition, no adherence to intestinal loops of the transplanted bladder or hydroureteronephrosis were observed in both groups of transplanted animals.

Continuous Cystometrogram

Figure-1 shows representative CMG tracings of an autotransplanted rat and of its respective control. Mean maximal intravesical pressure in autotransplanted rats was significantly lower than in control rats whereas mean duration of micturition and micturition intervals were not significantly different between control and autotransplanted rats (Figure-2 and Table-1). During the filling phase of the CMG, non-micturition contractions were not observed in either control or autotransplanted rats.

Figure-3 shows representative CMG tracings of control and syngeneic transplanted spontaneous hypertensive rats. Mean maximal

Figure 1 – Representative cystometric recordings of female Wistar rats which underwent bladder autotransplant. Non-operated rat (A) and rat 30 days after bladder autotransplant (B). The autotransplanted rat showed detrusor contractions, with amplitude of maximal pressure, micturition intervals and micturition duration similar to the normal rat. The threshold of the intravesical pressure was partially increased when compared with the recording of non-operated rat.

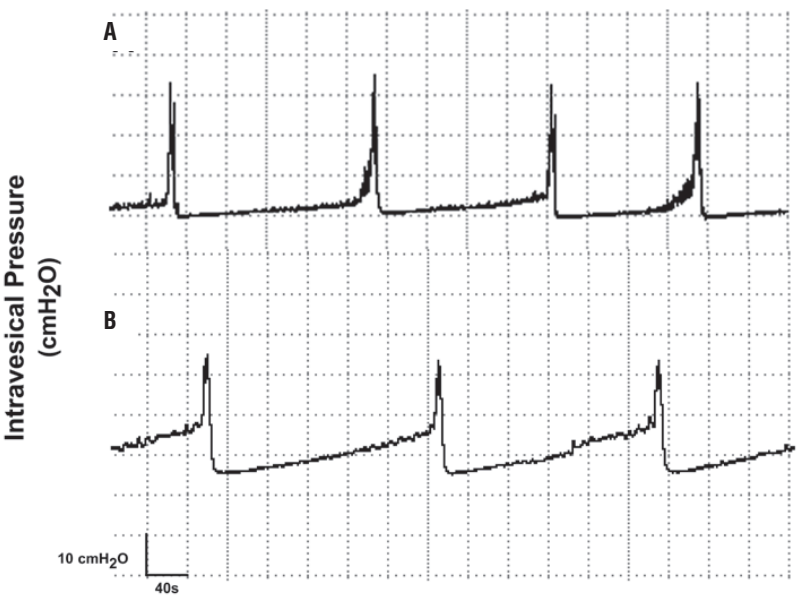
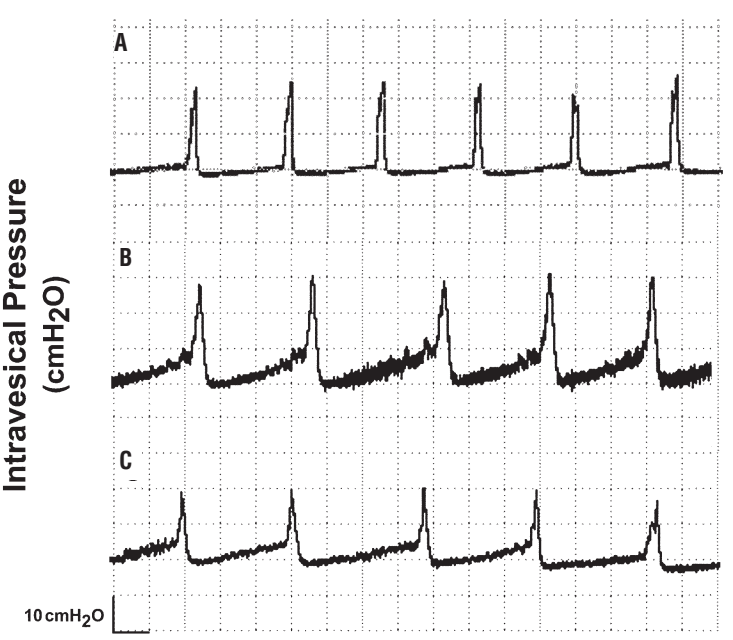


Figure 2 – Cystometric recordings of a female Wistar rat which underwent bladder autotransplant performed 30 days before. The rats were anesthetized with urethane for evaluation of the maximal pressure amplitude of the neobladder (A), micturition interval (B) and micturition duration (C). There was flow rate of bladder perfusion (0.9% saline solution, at 37 ºC) was 0.08 ml/min.

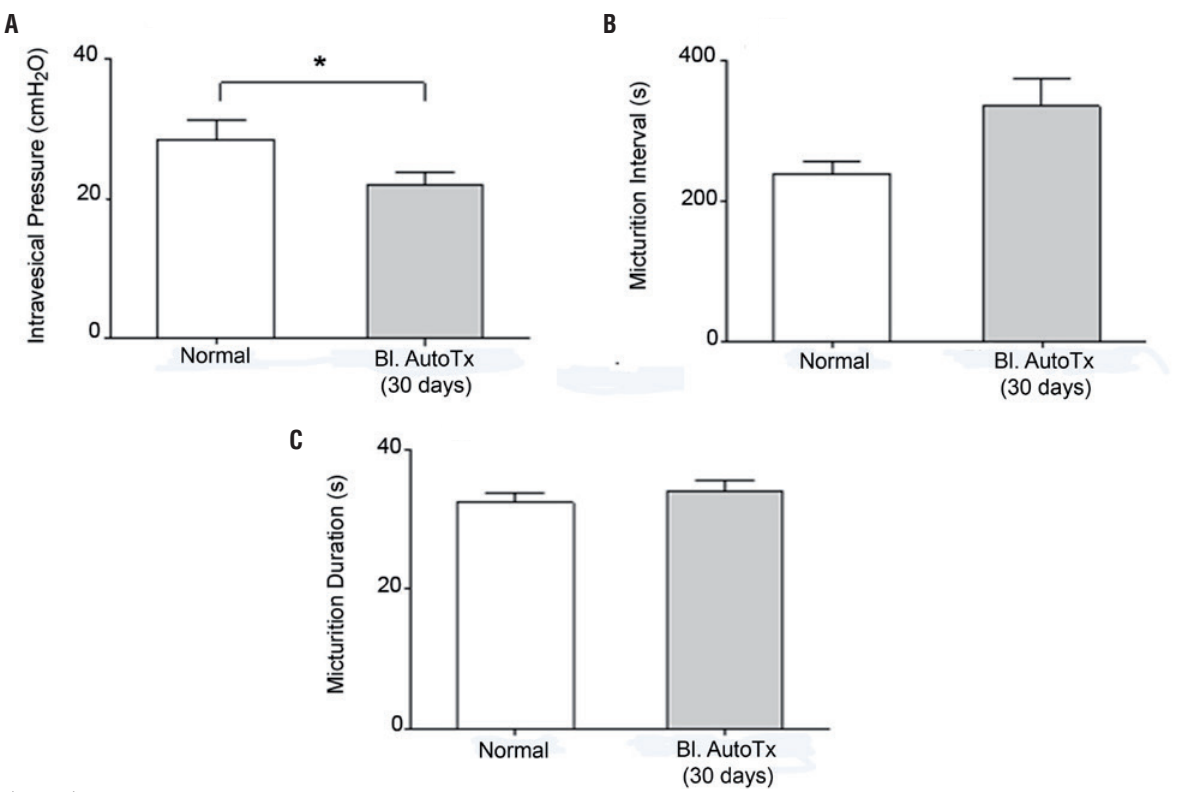


The asterisk indicates significant difference (P <0.05). Bl. = bladder; reimpl = autotransplant; d = days.

Table 1 - Cystometric values in female Wistar rats that underwent urinary bladder autotransplant.

	Control (n=5)	Bladder Autotransplant (n=5)
Intravesical Pressure (cmH_2O)	28.6 ± 2.7	23.0 ± 1.9
Micturition Interval (s)	238.1 ± 17.2	369.1 ± 25.5
Micturition Duration (s)	32.4 ± 1.3	34.1 ± 1.6

Figure 3 – Cystometric recordings of female Wistar rats which underwent bladder autotransplant performed 30 days after surgery. Evaluation of the maximal pressure amplitude of the bladder (A), micturition interval (B) and micturition duration (C). Flow rate of bladder perfusion (0.9% saline solution) was 0.08 ml/min (at 37ºC).

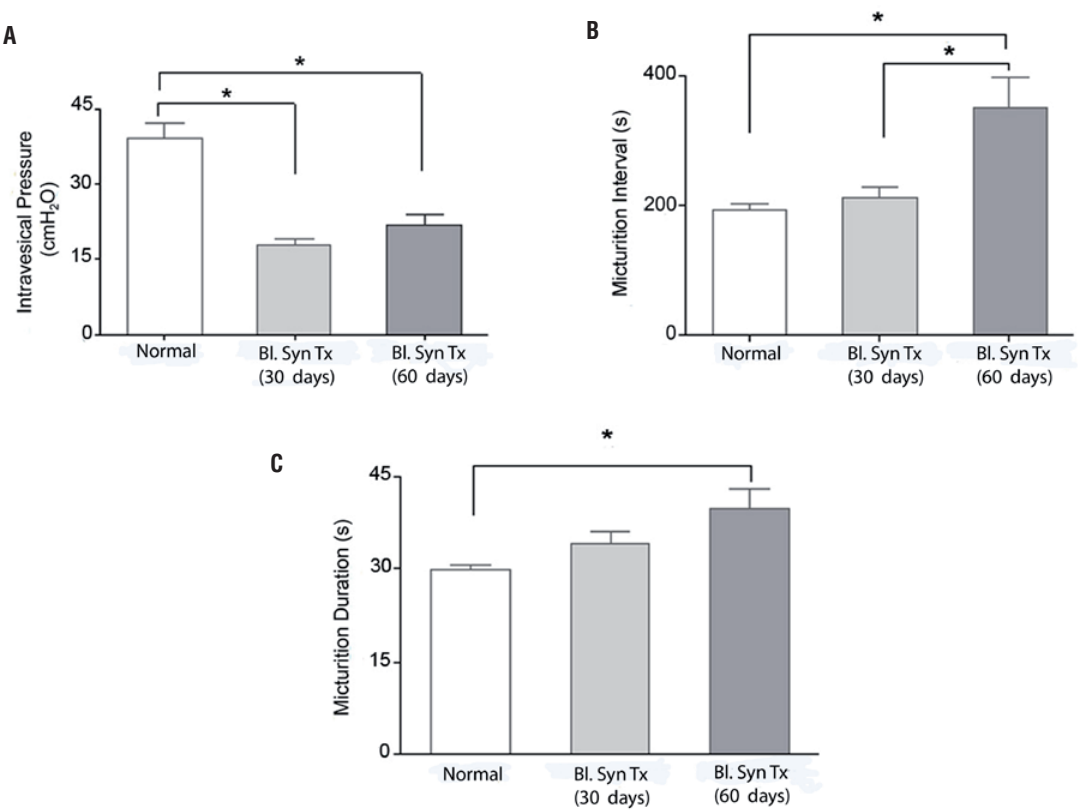


*(P <0.05).
Bl. = Bladder; AutoTx. = Autotransplant

intravesical pressure was significantly lower in the 30 and 60 day transplanted rats whereas mean micturition intervals were significantly different between normal rats and those 60 days after transplant and between rats 30 and 60 days after transplant, and mean micturition duration was significantly higher only in the 60 day transplanted animals (Figure-4 and Table-2). The data were also evaluated using Kolmogorov-Sminov test (KS) to test the Gaussian distribution. The results showed normal distribution.

The macroscopic configuration of neo-bladders was similar to the configuration of the normal bladder; the bladder wall was a little thicker but

Figure 4 – Cystomanometric recordings of female SHR rats which underwent bladder transplantation performed 30 and 60 days after surgery. The rats were anesthetized with urethane for evaluation of the maximal pressure amplitude of the bladder (A), micturition interval (B) and micturition duration (C). Flow rate of the bladder perfusion (0.9% saline solution) was 0.08 ml/min (at 37ºC).



The asterisks indicate
significant difference ($P < 0.05$).
Bl. = Bladder; Syn = Syngeneic; Tx = Transplant; d = days

Table 2 - Cystometric values in female spontaneous hypertension rats (SHR) that underwent urinary bladder syngeneic transplant .

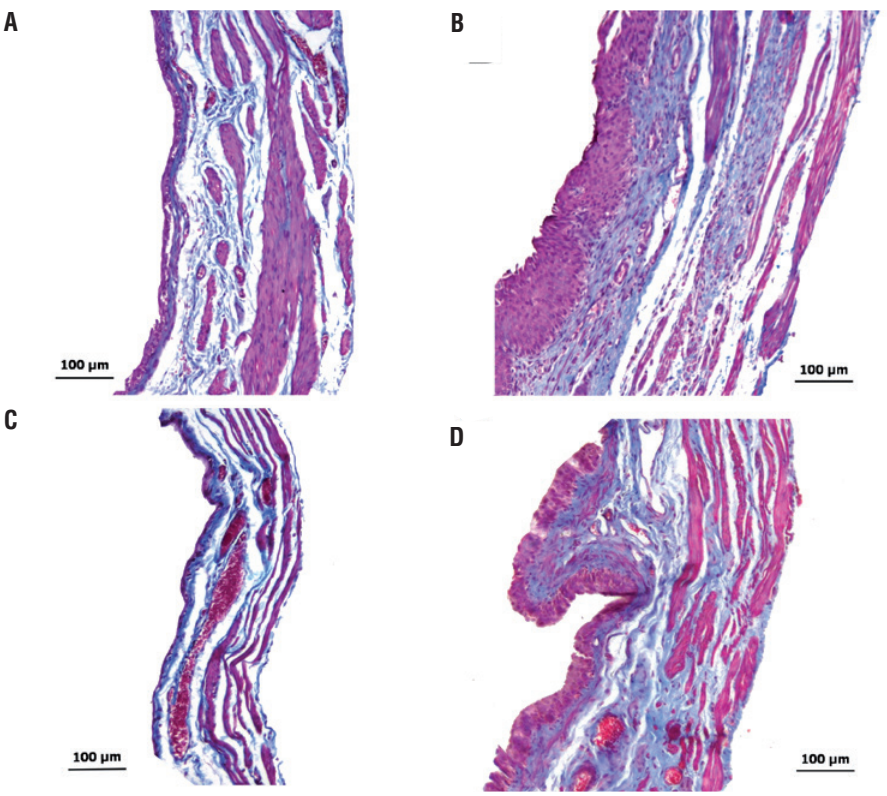
	Control (N=8)	Transplant (N=11) 30 Days	Transplant (N=6) 60 Days
Intravesical Pressure (cmH_20)	39.0 ± 3.1	18.3 ± 1.3	22.0 ± 1.9
Micturition Interval (s)	194.7 ± 8.5	214.0 ± 15.7	384.4 ± 25.8
Micturition Duration (s)	29.2 ± 0.9	34.1 ± 1.9	39.7 ± 3.3

without signs of shrinkage, fibrosis or graft encrustation. Microscopically both autotransplanted and syngeneic transplanted bladders showed thickening of the epitelium, lamina propria and muscle layers (Figure-5).

COMMENTS

The main finding of the present study consists in demonstrating that surgical procedures to transplant the supratrigonal bladder portion in

Figure 5 – Microphotography of sections of the bladder wall in female Wistar rats (A [control], B [autotransplanted bladder 30 days after surgery]), female SRH rats (C [control], and D [syngeneic transplanted bladder 30 days after surgery]). Different layers of the bladder wall show characteristics of preservation of the tissue, maintaining organization and architecture, without signs of fibrosis, wrinkles. There was increased thickening of the bladder wall, especially the epithelium which was thicker than that of the normal urinary bladder. Staining with Masson's trichrome occurred as described in the experimental protocol.



rats are entirely feasible. This surgical procedure was associated with the preservation of not only the anatomical architecture of the bladder but also with its functional integrity. Although a similar procedure was previously reported by Yamataka et al. (19) these authors did not perform any urodynamic measurements to assess the functional status of the transplanted bladders. The fact that the maximal intravesical pressure developed during the micturition contraction was slightly lower in both groups of transplanted animals suggests that the postganglionic parasympathetic detrusor innervation was partially restored after the transplantation. Nevertheless, the low pressure generated by the detrusor contraction was sufficient to promote complete voiding of the bladder.

The fact that the transplanted bladders remained viable suggests that the reestablishment of their blood supply, most likely through angiogenesis, occurred rapidly. Wrapping the neobladder with the omentum may also have contributed to the rapid recovery of the irrigation of the transplanted bladders; the capacity of the omentum to provide angiogenic factors has been reported previously (14, 19-21). Indeed, it was observed that the omentum adherence to the bladder wall showed numerous blood vessels entering the grafted bladder. In preliminary experiments, it was also observed that the viability of bladder transplant was greatly impaired when no omental pouch was created. In addition, the fact that the excised supratrigonal bladder portion was kept in cold saline

solution for only 30 min certainly contributed to the preservation and viability of the bladder tissue. Furthermore, total resorption of suture filaments and good cicatrization was observed in the suture site.

Since no surgical reconstruction of the blood vessels or nerve fibers of the autotransplanted or syngeneic transplanted bladder was performed, it is likely that endogenous angiogenic--(vascular endothelial growth factor-VEGF) and neurogenic-factors (nerve growth factor-NGF) were involved in the restoration of bladder irrigation and innervations (20-26) leading to the preservation of the micturition reflex.

CONCLUSIONS

The major finding of the present study is that in the rat, supratrigonal bladder transplant is a feasible surgical procedure associated with full recovery of the micturition reflex. In addition, since preserved bladder function implies vascular and nerve regeneration of the transplanted organ this procedure could also be useful as an experimental model to investigate the mechanisms involved in angiogenesis as well as in peripheral nervous system neurogenesis.

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CONFLICT OF INTEREST

None declared.

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Percutaneous tibial nerve stimulation versus electrical stimulation with pelvic floor muscle training for overactive bladder syndrome in women: results of a randomized controlled study

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ABSTRACT

Introduction: This study compared percutaneous tibial nerve stimulation (PTNS) versus electrical stimulation with pelvic floor muscle training (ES + PFMT) in women with overactive bladder syndrome (OAB).
Materials and Methods: 60 women with OAB were enrolled. Patients were randomized into two groups. In group A, women underwent ES with PFMT, in group B women underwent PTNS.
Results: A statistically significant reduction in the number of daily micturitions, episodes of nocturia and urge incontinence was found in the two groups but the difference was more substantial in women treated with PTNS; voided volume increased in both groups. Quality of life improved in both groups, whereas patient perception of urgency improved only in women treated with PTNS. Global impression of improvement revealed a greater satisfaction in patients treated with PTNS.
Conclusion: This study demonstrates the effectiveness of PTNS and ES with PFMT in women with OAB, but greater improvements were found with PTNS.

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INTRODUCTION

Overactive bladder syndrome (OAB) is a chronic disease characterized by urinary urgency with or without urge incontinence, frequency and nocturia (1, 2). The prevalence of OAB in the general population is reported to be 14-16% (3, 4). The total cost for diagnosis and treatment of OAB in the USA, during 2000 was estimated to be about USD 12.6 billion, which is comparable to the cost of osteoporosis and gynecologic and breast cancers (4). Pelvic floor muscle training (PFMT) and electrical stimulation (ES) are some of the less invasive procedures for treating OAB symptoms. Therefore, they are used as first treatments (5-7). Percutaneous tibial nerve stimulation (PTNS) is a minimally invasive and effective therapy used both as first-line treatment, as well as in managing of unresponsive patients (8, 9). Nevertheless, in common practice, antimuscarinic agents are frequently used as first treatment although burdened by a low adherence and although these

patients need protracted treatment with periodic controls. The aim of this study was to compare efficacy, safety, quality of life and patient's satisfaction parameters in patients treated with two different therapies for OAB symptoms.

MATERIALS AND METHODS

From September 2014 to May 2015, 60 consecutive women (mean age: 58.5 years, range 38-72) with OAB syndrome were enrolled in this randomized controlled study. All subjects previously underwent a detailed clinical evaluation, including a complete history and physical examination. Patients with stress incontinence, urinary tract infection, neurological disease, bladder lithiasis, genital prolapse higher than stage II on POP-Q system, pregnancy, diabetes mellitus, a history of anti-incontinence surgery and/or prolapse repair, pelvic tumors and previously treated with radiation therapy or antimuscarinic agents, and patients who were not cooperative, were excluded. The study was approved by the local ethics committee and all patients signed informed consent before starting treatment. Women were divided randomly into two groups of 30 patients each using online randomization (GraphPad QuickCalcs software: http://www.graphad.com/quickcalcs/randomize1) by an independent biostatistician who was unaware of treatments performed by patients and was not involved in the study. In group A, women underwent pelvic floor rehabilitation. The treatment consisted of ten sessions of electrical stimulation (ES) followed by pelvic floor muscle training (PFMT). The sessions were performed three times a week for one hour. ES was applied in short-term mode with vaginal probe for 30 minutes using biphasic square waves with 20Hz frequency for 30 sec., alternating at 5Hz also for 30 sec. Every seat was individually followed by a physiotherapist and patients were carefully instructed to perform a correct pelvic muscle contraction. After the ten sessions, the patients continued the exercises at home for six months. In group B, the women underwent PTNS twice a week for 30 min each for a total of 6 weeks. All patients were assessed one month after the end of the treatments performed at the physiotherapy clinics.

Endpoints

Reduction in number of voids per 24 hours was considered the primary efficacy endpoint in this study. Secondary endpoints were: reduction in number of episodes of urge incontinence, reduction of episodes of nocturia, changes in patient perception of intensity of urgency, impact of OAB symptoms on patient's quality of life and evaluation of improvement: number of voids per 24 hours, episodes of nocturia and urge incontinence were evaluated using a 3-day micturition diary. The Overactive Bladder questionnaire Short Form (OAB-q SF) was used to assess the impact of OAB symptoms on patient's quality of life. The questionnaire consists of 6 items related to symptoms with 6 possible options ranging from "not at all" (score 1) to "a very great deal" (score 6), and a health-related quality of life scale with 13 items, with 6 response options ranging from "none of the time" (score 1) to "all of the time" (score 6). Urgency was assessed by the Patient Perception of Intensity of Urgency Scale (PPIU-S) consisting of a 5-point scale from 0 (no urgency) to 4 (urge incontinence). Improvement was evaluated with the Patient Global Impression of Improvement questionnaire (PGI-I). The PGI-I is a validated generic tool for assessment of the overall improvement or deterioration that patients experience following the treatment. It is a 7-point scale from "very much improved (score 1), to "very much worse" (score 7). The micturition diary, OAB-q SF and PPIU-S, were completed before and after treatment. PGI-I was performed only at the end of treatment.

Statistical analysis

Statistical analysis was performed using the MedCalc software package (version 14.12.0). Data are expressed as means±SD. Comparisons were carried out using the Wilcoxon test for paired samples, the Mann-Whitney for independent samples and the Chi square test (X2 test). A p value of <0.05 was considered significant. Data were assessed by a researcher not involved in the study protocol.

RESULTS

All 60 patients enrolled in the two groups were evaluable at the end of the study. No significant

side effects were found with the two treatments. A reduction in the number of daily micturitions was found both with ES+PFMT and with PTNS with a significant difference in the group of patients undergoing PTNS (Table-1). Anyway, the number of daily micturitions did not show significant differences when comparing the results obtained after therapy in the two groups of patients (Table-1). Nocturia and urge incontinence showed improvements in both groups with significant differences only in patients treated with PTNS. Also, when the two groups were compared after treatment, women treated with PTNS showed statistically significant improvement compared to those treated with ES+PFMT (Table-1). Voided volume significantly improved in the two groups of patients with more evident results in the group treated with PTNS, also in the post treatment comparison. The quality of life of patients evaluated with OAB--q SF showed significant improvements in groups, both with ES+PFMT and with PTNS (Table-2). When comparing post treatment data, patients treated with PTNS showed better results than those treated with ES+PFMT. Improvements were found in PPIU-S in the two groups of patients with a statistically significant difference in women undergoing PTNS when the two groups were compared following treatment (Table-2). The PGI-I showed improvements in both groups of patients, with a significant difference in women treated with PTNS (Table-2).

DISCUSSION

Less invasive procedures represent the first-line treatment recommended by the Consensus Con-

Table 1 - 3-day micturition diary.

	Group A FISIO		Group B SANS	
Patients, n	30		30	
Mean age	57.31		59.69	
Median (range)	60 (38-69)		62 (40-72)	
Daily micturition	**Before**	**After**	**Before**	**After**
Mean±SD	11.15±2.07	9.03±1.68	11.25±1.13	9.00±2.02
Median (range)	9 (7-18)	9 (6-12)	11 (9-14)	9 (6-13)
p	0.0620		0.0307	
After Group A vs. After Group B: p=0.3758				
Nocturia	**Before**	**After**	**Before**	**After**
Mean±SD	2.62±1.00	1.54±0.93	2.50±1.02	1.45±1.02
Median (range)	3 (1-4)	2 (0-3)	3 (0-4)	2 (0-3)
p	0.1683		0.0201	
After Group A vs. After Group B: p=0.049				
Urge incontinence	**Before**	**After**	**Before**	**After**
Mean±SD	2.54±0.63	2.00±0.68	3.05±0.97	1.45±1.00
Median (range)	3 (1-3)	2 (1-3)	3 (0-4)	2 (0-3)
p	0.1293		0.0009	
After Group A vs. After Group B: p=0.0251				
Voided Volume (*)	**Before**	**After**	**Before**	**After**
Mean±SD	136.75±11.92	157.92±10.30	140.21±13.50	171.42±12.68
Median (range)	133.5(115-160)	155 (140-180)	135 (120-165)	175 (145-190)
p	0.0048		0.0003	
After Group A vs. After Group B(**): p=0.0222				

(*) Wilcoxon test for paired samples
(**) Mann-Whitney for independent samples

Table 2 - Overactive Bladder questionnaire Short Form (OAB-qSF), Patient Perception of Intensity of Urgency Scale (PPIUS) and Patient Global Impression of Improvement questionnaire (PGI-I).

	Group A		Group B	
Patients, n	30		30	
OAB-qSF (6 items)(*)	**Before**	**After**	**Before**	**After**
Mean±SD	19.46±3.13	15.77±5.48	21.35±2.57	12.90±2.93
Median (range)	20 (14-24)	16 (8-28)	22 (14-25)	13.5 (6-18)
p	0.0420		<0.0001	
After Group A vs. After Group B (**): p=0.0172				
OAB-qSF (13 items) (*)	**Before**	**After**	**Before**	**After**
Mean±SD	36.85±13.02	29.38±9.32	44.40±8.51	24.85±5.96
Median (range)	39 (15-54)	29 (14-50)	45.5 (22-64)	24 (12-39)
p	0.0420		<0.0001	
After Group A vs. After Group B (**): p=0.0295				
PPIUS	**Before**	**After**	**Before**	**After**
Mean±SD	2.77±0.80	2.00±0.68	3.00±0.63	1.75±0.77
Median (range)	3 (2-4)	2 (1-3)	3 (1-4)	2 (1-3)
p	0.1014		0.0001	
After Group A vs. After Group B: p=0.0459				
PGI-I	**Before**	**After**	**Before**	**After**
Mean±SD	2.85±0.36		2.30±0.78	
Median (range)	3 (2-3)		2 (1-4)	
p	0.0415			

(*) Wilcoxon test for paired samples
(**) Mann-Whitney for independent samples

ference on Urinary Incontinence in Adults and by the guidelines of the American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (AUA/SUFU) for therapy of OAB (5, 6). However, in common practice, antimuscarinic agents are frequently the first treatment considered for treating OAB (6), but results have shown that a high percentage of patients treated with these drugs discontinued therapy (10-13).

Pelvic floor muscle training (PFMT) was popularized by Arnold Kegel in 1946 for the management of urinary incontinence (14), and then it was also used in the treatment of urge incontinence and overactive bladder (15). Pelvic floor muscle contraction can be used to occlude the urethra and prevent urine loss during detrusor contraction but it can improve bladder control by inhibiting or suppressing bladder contraction which also changes the patient's behavior (16). PFMT was used alone or in combination with behavioral and cognitive therapy (6), vaginal cones, bladder training, ES, drug treatment, continence pessary, heat and steam generating sheet (HSGS) (17) and assisted with EMG-biofeedback (18). PFMT has shown good results in reducing urge incontinence, urinary frequency and nocturia (15, 18-21). ES was particularly effective in the treatment of OAB symptoms (20) and is considered by some authors to be more effective than drug treatment, permitting an effective reduction or inhibition of detrusor activity by stimulating afferents of the pudendal nerve (22). PTNS is a form of "neuromodulation" (23); it is a safe, minimally invasive and effective treatment for managing refractive OAB (9, 23). Randomized studies comparing PTNS versus anticholinergic agents have shown that the efficacy of PTNS is comparable or superior to anticholinergic agents in controlling OAB symptoms but with a better side effect profile (8, 24-28). To our

knowledge, studies carried out comparing percutaneous tibial nerve stimulation with pelvic floor muscle training and electrical stimulation are not described in the literature. The results of this study relate to the short term efficacy of these two different treatments. The data obtained, even though carried out on a moderate number of patients, highlight a complete adherence by all the women to the performed treatments. This is a result that should be emphasized as it is a chronic symptom for which great adherence to therapy is required by patients. These results are due mainly to the total absence of side effects. Furthermore, the low cost to patients of the therapy and the constant and reassuring presence, during treatments, of a physiotherapist or medical specialist, represent important factors in patients who often have psychological problems secondary to OAB. Improvements were found in both groups in all symptoms evaluated with 3-day micturition diary, but PTNS showed greater effectiveness than ES+PFMT. When evaluating results obtained following therapy in the two groups of patients, PTNS showed statistical significant improvements compared to women treated with ES+PFMT in all parameters except daily micturition, which in any case registered greater results in patients treated with PTNS. In the same way, the data obtained by comparing completed questionnaires also confirmed better results with statistically significant improvements in patients treated with PTNS.

CONCLUSIONS

ES and PFMT represent some of the less invasive but effective procedures recommended for OAB treatment. In common practice, PTNS is a procedure used especially when other treatments have failed. For its effectiveness and its minimal invasiveness PTNS should be considered as a first-line treatment.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Does MRI help in the pre – operative evaluation of pelvic fracture urethral distraction defect? – a pilot study

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ABSTRACT

Objectives: To study the usefulness of MRI in preoperative evaluation of PFUDD. Can MRI provide additional information on urethral distraction defect (UDD) and cause of erectile dysfunction (ED)?

Materials and Methods: In this prospective study, consecutive male patients presenting with PFUDD were included from Feb 2011 till Dec 2012. Those with traumatic spinal cord injury and pre-existing ED were excluded. Patients were assessed using IIEF questionnaire, retrograde urethrogram and micturating cystourethrogram (RGU+MCU) and MRI pelvis. Primary end point was erectile function and secondary end point was surgical outcome.

Results: Twenty patients were included in this study. Fourteen patients (70%) were ≤40years; fifteen patients (75%) had ED, seven patients (35%) had severe ED. MRI findings associated with ED were longer median UDD (23mm vs. 15mm, p=0.07), cavernosal injury (100%, p=0.53), rectal injury (100%, p=0.53), retropubic scarring (60%, p=0.62) and prostatic displacement (60%, p=0.99). Twelve patients (60%) had a good surgical outcome, five (25%) had an acceptable outcome, three (15%) had a poor outcome. Poor surgical outcome was associated with rectal injury (66.7%, p=0.08), cavernosal injury (25%, p=0.19), retropubic scarring (18.1%, p=0.99) and prostatic displacement (16.7%, p=0.99). Five patients with normal erections had good surgical outcome. Three patients with ED had poor outcome (20%, p=0.20).

Conclusions: MRI did not offer significant advantage over MCU in the subgroup of men with normal erections. Cavernosal injury noted on MRI strongly correlated with ED. Role of MRI may be limited to the subgroup with ED or an inconclusive MCU.

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INTRODUCTION

Posterior urethral injury complicates up to 25% of pelvic fractures arising from blunt pelvic trauma (1). Since majority of patients with traumatic urethral injuries are younger than 40 years, ED is a devastating complication encountered in up to 54% of these individuals (2, 3). Patients with PFUDD (pelvic fracture urethral distraction defect) are routinely evaluated with combined RGU (retrograde urethrogram) and MCU (micturating cystourethrogram). Their limitations include the 2 dimensional images and the non-visualization of prostatic urethra in some patients. MRI pelvis can

be helpful in studying the distorted pelvic anatomy and planning surgical approach as well as to help evaluation of erectile dysfunction (4-6). It has been suggested that certain MRI findings have a higher association with ED (7). MR urethrogram has been suggested to show structural details of urethra as well as periurethral tissues with 3-dimensional orientation (8).

The purpose of this study was to find out whether MRI imaging would offer any additional information helpful in the pre-operative planning, counseling and management of PFUDD, especially in the subgroup of men with ED.

MATERIAL AND METHODS

Study design

A prospective study was carried out between February 2011 and December 2012. Following Institutional Review Board and Ethics Committee approval, consecutive men presenting with pelvic fracture urethral distraction defect (PFUDD) scheduled for primary urethral reconstruction were recruited in this study. Patient with traumatic spinal cord injury, pre-existing ED, previous operative interventions for PFUDD, co-morbid conditions like diabetes and hypertension with end organ damage were excluded.

Pre-operative evaluation

Erectile function was assessed using a validated questionnaire (International Index of Erectile Function-IIEF); MRI pelvis was performed prior to urethral reconstruction. Patients were classified according to the Erectile Function domain of International Index of Erectile function (IIEF-EF) into three groups: normal erectile function (≥25), mild to moderate ED [7-24] and severe ED (≤6). The final comparison was done between those with normal erectile function and those with ED (moderate and severe ED).

MRI pelvis

MRI pelvis was done using Philips intera achieva 3.0 tesla. Anterior urethra was distended with normal saline using a 12Fr. Foley catheter placed under aseptic precautions with a partially inflated bulb (0.5-1mL) placed at the fossa navicularis. 2% Xylocaine jelly was used for local anaesthesia. Suprapubic catheter was clamped 30 minutes prior to the study to allow natural distension of the bladder. The image series obtained included: T2WI sagittal, axial, coronal; STIR_Long TE/RA, SshTSE, SPAIR, SENSE. TR: 3500ms, TE 90.0ms, ST 3.0mm. The following parameters were assessed by the same radiologist: length of urethral defect (Figures 1A and B) (distance between prostatic apex and the most proximal portion of the bulbar urethra), direction of prostatic displacement (Figures 1C and D) (superior, posterior, or lateral), and extent of scar tissue (Figure-1E) (retropubic, prostatic, peri-prostatic, or subprostatic). Presence of bladder base fistula, rectal injury or cavernosal injury (Figure-1F) was documented.

Surgical outcome

The operative outcome was categorized into 3 groups based on the previously published data from this department (9). The 3 groups were: good outcome with Qmax >15mL/sec, acceptable outcome with Qmax >15mL/sec after a single endoscopic internal urethrotomy and failure when Qmax <15mL/sec. Further comparisons were made between MRI findings, erectile function and surgical outcome.

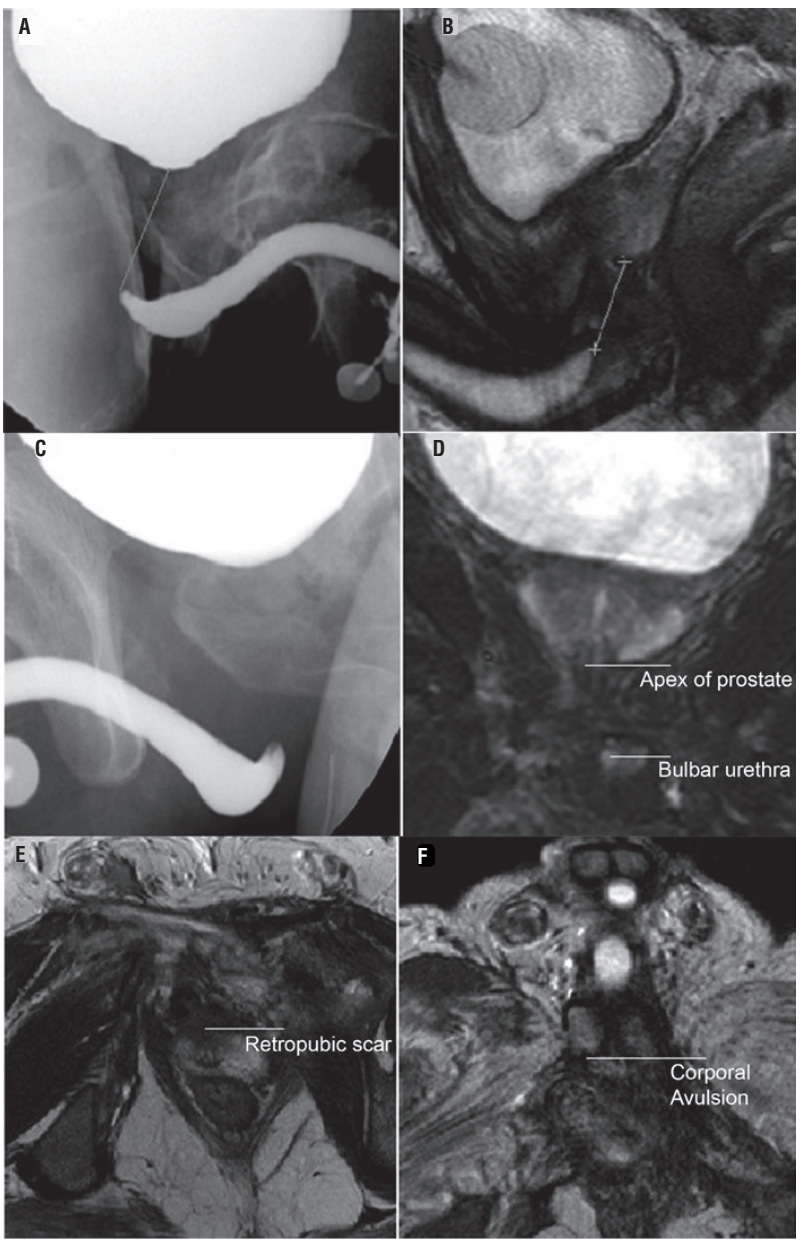
Statistical analysis

Statistical analysis was performed using SPSS version 16 (IBM Corporation, USA). All categorical variables were summarized as counts and percentages and continuous variables as mean and standard deviation or Median and Range. Fisher's exact test was used for testing the association between categorical variables and Wilcoxon rank sum test was used for comparing non-normally distributed continuous variable by groups.

RESULTS

Twenty patients with traumatic posterior urethral injury were recruited during the study period. The median age at presentation was 34 years, (range of 17-61 years) (Table-1). Road traffic accident was the mode of injury in 18 (90%) patients. All patients underwent trocar suprapubic

Figure 1 - The figure shows urethral defect on MCU (A) and MRI (B); prostatic displacement on MCU (C) and MRI (D); retropubic scarring on MRI (E); and corporal avulsion on MRI (F).



catheterization with 14Fr Foley's catheter during the emergency admission. None had undergone an attempt of primary realignment. Three who had associated anorectal injuries underwent diversion colostomy. Pelvic fracture type A was the commonest (11/20). One patient underwent external fixation of pelvic fracture. Urethral reconstruction was performed after 3 months. Evaluation using IIEF questionnaire showed ED in 15 patients (75%), while 7 patients (35%) had severe ED.

Urethral distraction defect (UDD)

The posterior urethra was not visualized in 4 men; in this study all 4 patients had ED. The

Table 1 - Baseline characteristics of patients with pelvic fracture urethral distraction defect (n=20).

Baseline characteristic	Value	Number (%)
Age at presentation (years)	Median (range)	34 (17-61)
	<40 years (%)	14 (70.0)
Mode of injury	Road traffic accidents	18 (90.0)
	Fall from train	1 (5.0)
	Crushed by collapsing wall	1 (5.0)
Type of pelvic fracture	Tile A	11 (55.0)
	Tile B	2 (10.0)
	Tile C	7 (35.0)
IIEF score (EF domain)	Normal (25-35)	5 (25.0)
	Moderate erectile dysfunction (7-24)	8 (40.0)
	Severe erectile dysfunction (≤6)	7 (35.0)

median UUD on MCU in those with ED was longer than those with normal erectile function (40mm vs. 13mm, p=0.039). The median UUD on MRI in those with ED was longer than those with normal erectile function (23mm vs. 15mm, p=0.07). The median intra-op UDD correlated with median MRI UDD more than the median MCU UDD; especially in those with erectile dysfunction (20mm vs. 23mm vs. 40mm).

MRI findings

Prostatic displacement was present in 12 patients (60%). Retropubic scarring was seen in 11 patients (55%). Injury to corpora cavernosa was seen in 4 patients (20%) (Figure-1). Three patients (15%) had recto-urethral fistula. About 90% of patients with ED had either retropubic scarring or prostatic displacement. MRI findings associated with ED were cavernosal injury (100%, p=0.53), rectal injury (100%, p=0.53), retropubic scarring (60%, p=0.62) and prostatic displacement (60%, p=0.99), though this did not reach statistical significance. ED was seen in all patients with either cavernosal injury or rectal injury. The MRI findings did not change the surgical management.

Surgical outcome

All twenty patients underwent anastomotic urethroplasty by progressive perineal approach. Twelve patients had a good operative outcome. Five patients with poor flow had soft strictures, requiring cystoscopy and dilation once as outpatient. They were advised self calibration. Subsequently, they had a satisfactory urine flow with Qmax >15mL/sec. Three patients failed to void normally following catheter removal. They all underwent suprapubic catheter placement. Two patients underwent a redo anastomotic urethroplasty with good outcome. Third patient was lost to follow-up.

All five patients who reported normal erectile function post trauma had good surgical outcome. Seven (46.7%) out of the fifteen patients with ED had a good outcome, while five patients (33%) had an acceptable outcome and three patients (20%, p=0.20) had a poor outcome. MRI findings were compared with the surgical outcome (Table-2). MRI findings associated with poor surgical outcome were rectal injury (66.7%, p=0.08), cavernosal injury (25%, p=0.19), retropubic scarring (18.1%, p=0.99) and prostatic displacement

Table 2 - Comparison of surgical outcome with erectile function and MRI findings (n=20).

	Surgical Outcome			P value‡
	Good (n=12)	Acceptable (n=5)	Failure (n=3)	
Erectile function				
Normal (n=5)	5 (100.0)	0	0	0.20
Moderate and Severe ED (n=8)	7 (46.7)	5 (33.3)	3 (20.0)	
MRI findings				
Retropubic scarring (n=11)				
Yes	6 (54.6)	3 (27.3)	2 (18.1)	0.99
No	6 (66.7)	2 (22.2)	1 (11.1)	
Prostatic displacement (n=12)				
Yes	7 (58.3)	3 (25.0)	2 (16.7)	0.99
No	5(62.5)	2 (25.0)	1 (12.5)	
Cavernosal Injury (n=4)				
Yes	1 (25.0)	2 (50.0)	1 (25.0)	0.19
No	11 (68.9)	3 (18.8)	2 (12.5)	
Rectal injury (n=3)				
Yes	1 (33.3)	-	2 (66.7)	0.08
No	11 (64.7)	5 (29.4)	1 (5.9)	

‡ p value is obtained using fisher's exact test

(16.7%, p=0.99). Two out of three patients with rectal injury had poor surgical outcome, though this did not reach statistical significance.

DISCUSSION

Younger age of presentation noted in our study correlated with the review by Kulkarni et al. They found higher proportion of children and adolescents presenting with PFUDD in India when compared to Italy (25.6% vs. 8%) (10). Urethral distraction defects occur mainly in Tile B and C pelvic fractures (11). In our study, Tile A was the commonest. ED was defined by NIH consensus development conference as "the inability to achieve an erect penis as part of overall multifaceted process of male sexual performance, pelvic fracture being a major risk factor" (12, 13). In a cross-sectional study of male sexual function after pelvic ring fractures using the International Index for Erectile Function (IIEF), pubic diastasis was related to impaired erectile function and overall satisfaction (14).

High incidence of ED (75%) in this group was comparable with the study by Shenfeld et al. (15) in which 72% had ED. Anger et al. reported ED of some degree in 54% of patients with PFUDD and severe ED in 30% (3). Corriere et al. reported prevalence of ED following trauma as 25% (50/197) (16). Koraitim reported prevalence of ED after traumatic posterior urethral injury in 44 out of 110 (40%) patients who were sexually potent (14). King reported prevalence of ED in 42% of patients with PFUDD when compared to

5% of patients with pelvic fracture alone (17). Introduction of validated IIEF questionnaire in 1997 has helped in a more objective and detailed assessment of erectile dysfunction (18). Lack of such objective assessment in the past could explain the wide variation in the prevalence of erectile dysfunction prior to this. Evaluation of nocturnal tumescence and rigidity has revealed ED in up to 84% (19). The cause of ED following PFUUD was speculated to be neurovascular injury (15). Mark et al. reviewed 92 patients and found ED in 62%. Urethral reconstruction did not lead to ED in potent man. In those who had ED, self-injection using intracavernous vasoactive drugs was successful in 24 out of 27 patients (89%), which could suggest that the etiology was neurological (20).

In a review of MRI done on 27 patients with PFUDD by Narumi et al., 95% of those with corporal avulsion had ED while 83% had normal erection in the absence of these findings (4). In another study by Koraitim et al., 21 patients with PFUDD were assessed using MRI combined with antegrade urethrography. They found avulsion of cavernosa from the ischium as well as lateral displacement of prostate in all patients with ED (7). Proximity of cavernosal nerves and internal pudendal arteries to the prostatic apex makes this observation interesting (15). In our study, MRI showed prostatic displacement in 12 patients and injury to corpora cavernosa in 4 patients. Erectile dysfunction was present in all patients with cavernosal injury. ED caused by cavernosal injury is unlikely to respond to pharmacological interventions and would require penile prosthesis. This has a significant impact on pre-operative counselling and management of ED.

MRI helps identify the exact urethral distraction defect especially when the posterior urethra is not visualised on micturating cystourethrogram. The degree and direction of prostatic displacement becomes evident. MRI also reveals the presence of concomitant rectal injury. MR urethrogram has been reported to be more reliable than combined RGU and MCU in measuring the length of obliterative urethral strictures (21). This was noted in our study in the subgroup of men with erectile dysfunction and when prostatic urethra was not visualized on MCU. MRI has been suggested to have a significant impact on pre-op decision making, counselling and the appropriate surgical approach (7). This was not seen in our study.

MRI provides detailed three-dimensional images of the urethral distraction defect. In men with normal erections, MRI findings did not have a significant impact on the pre-operative decision making or counselling. In those with erection dysfunction, presence of cavernosal injury noted on the MRI added value to preoperative counselling and management of ED. Disadvantages of MRI pelvis include the higher cost, contraindication in those with ferromagnetic implants and longer duration of study in enclosed space. Considering these factors, there is little advantage of preoperative MRI in the evaluation of PFUDD in men with normal erections when the posterior urethra was visualized on MCU. Presence of ED based on the IIEF questionnaire and non-visualization of posterior urethra on MCU can help us decide on the use of preoperative MRI in PFUDD.

Although our study includes a small group of patients, we believe that this prospective study gives directions for further research.

CONCLUSIONS

MRI provides detailed three-dimensional images of the urethral distraction defect. MRI did not offer significant advantage over MCU in the pre-operative evaluation of PFUDD in the subgroup of men with normal erection. Cavernosal injury noted on MRI strongly correlated with ED, added value to pre-operative counseling and management of ED. Role of MRI may be limited to the subgroup with ED and those with non-visualized posterior urethra on MCU.

ABBREVIATIONS

ED = Erectile dysfunction
IIEF = International Index of Erectile Function
MCU = Modern contraceptive use
MRI = Magnetic resonance imaging
PFUDD = pelvic fracture urethral distraction defect
RGU = Retrograde urethrogram
UDD = Urethral distraction defect

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A prospective randomized controlled multicentre trial comparing intravesical DMSO and chondroïtin sulphate 2% for painful bladder syndrome/interstitial cystitis

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ABSTRACT

Objective: To compare effectiveness of intravesical chondroïtin sulphate (CS) 2% and dimethyl sulphoxide (DMSO) 50% in patients with painful bladder syndrome/interstitial cystitis (PBS/IC).

Materials and methods: Patients were randomized to receive either 6 weekly instillations of CS 2% or 50% DMSO. Primary endpoint was difference in proportion of patients achieving score 6 (moderately improved) or 7 (markedly improved) in both groups using the Global Response Assessment (GRA) scale. Secondary parameters were mean 24-hours frequency and nocturia on a 3-day micturition dairy, changes from baseline in O'Leary-Sant questionnaire score and visual analog scale (VAS) for suprapubic pain.

Results: Thirty-six patients were the intention to treat population (22 in CS and 14 in DMSO group). In DMSO group, 57% withdrew consent and only 6 concluded the trial. Major reasons were pain during and after instillation, intolerable garlic odor and lack of efficacy. In CS group, 27% withdrew consent. Compared with DMSO group, more patients in CS group (72.7% vs. 14%) reported moderate or marked improvement (P=0.002, 95% CI 0.05-0.72) and achieved a reduction in VAS scores (20% vs. 8.3%). CS group performed significantly better in pain reduction (-1.2 vs. -0.6) and nocturia (-2.4 vs. -0.7) and better in total O'Leary reduction (-9.8 vs. -7.2). CS was better tolerated. The trial was stopped due to high number of drop-outs with DMSO.

Conclusions: Intravesical CS 2% is viable treatment for PBS/IC with minimal side effects. DMSO should be used with caution and with active monitoring of side effects. More randomized controlled studies on intravesical treatments are needed.

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INTRODUCTION

Because interstitial cystitis (IC) varies so much in symptoms and severity, most experts believe it is not one, but several diseases. In recent years, scientists have started to use the terms painful bladder syndrome (PBS) or bladder pain syndrome (BPS) to describe cases with painful urinary

symptoms that may not meet the strictest definition of IC. IC can be considered as a subgroup of patients in whom cytoscopic findings can be noted. Painful bladder syndrome (PBS) is a chronic bladder condition characterized by chronic pelvic pain, pressure or discomfort perceived to be related to the bladder and accompanied by at least one urinary symptom, such as increased urinary urgency or frequency. The European Society for the Study Interstitial cystitis (ESSIC) decided to refer to the condition with the term "painful bladder syndrome/interstitial cystitis (PBS/IC)" (1). The American Urological Association (AUA) Guidelines Committee refers to an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms with a duration of at least 6 weeks, in the absence of any confusable diseases that may give rise to the symptoms (2, 3). The etiology of PBS/IC is still not well understood. To date, there is a general agreement on the administration of some oral or intravesical drugs (4, 5). With regard to intravesical therapy, it has been hypothesized that the urothelial mucin glycosaminoglycan (GAG) layer which protects the urothelial cells is damaged in PBS/IC (6, 7). Intravesical treatment with DMSO, chondroïtin sulphate, hyaluronic acid and heparin have been used to repair the GAG layer with variable clinical success (6-8). Dimethyl sulphoxide (DMSO, Rimso-50) is the only drug approved by the U.S. Food and Drug Administration (FDA) for intravesical treatment of PBS/IC. Only one small, short, single-center trial has reported efficacy (9). The EAU Guidelines on chronic pelvic pain updated in April 2014 underline that DMSO has been used in the past but there is insufficient current evidence to recommend its use (10). Chondroïtin sulphate (CS), an important component of the GAG layer seems to be promising, but comparative data with other therapies are lacking (11-13). A 2.0% solution of sodium CS in phosphate buffered saline (chondroïtin sulphate, Tribute Pharmaceuticals, Milton, ON) has been approved in Canada and Europe for intravesical treatment of PBS/IC. Assessing the outcome of such treatments is difficult. Objective parameters such as daytime and nighttime frequency may not always reflect the impact of the condition on the life of the patient. Patient reported outcome parameters are more frequently used to assess treatments in overactive bladder disease and in painful bladder research. Several validated questionnaires can be used to assess patients with PBS/IC. One of the most frequently used is the O'Leary-Sant questionnaire. Next to this questionnaire, the Global Response Assessment can be used. This is a validated 7 point Likert scale comparing the current status of the patient to the pre-intervention status. This scale has been used in several other studies on PBS/IC (11, 14-18). For the assessment of suprapubic pain the visual analog scale (VAS) was used. The aim of this study was to compare the clinical effectiveness of intravesical chondroïtin sulphate 2% (Uracyst™) and DMSO 50% in the treatment of patients with PBS/IC.

MATERIALS AND METHODS

Patients and study design

The study was designed as a prospective randomized multicenter evaluation of PBS/IC patients who were randomized to receive either 6 weekly instillations of CS 2% (treatment arm) or DMSO 50% (control arm). Four centers participated between January 2012 and January 2015, each center enrolling a similar number of patients. To detect a 0.75 difference on the 7 point Likert scale, with 80% power at 0.05% significance, 45 patients were needed in each group.

Candidates for inclusion in the study were men and women aged 18-75 years with a history of symptoms of bladder pain/discomfort described as suprapubic pain related to bladder filling, accompanied by other symptoms such as daytime and/or nighttime frequency in the absence of infection or other pathology. All patients underwent urodynamic evaluation and cystoscopy with an evidence of early bladder sensation and low maximum bladder capacity. We considered in this study also patients with negative macroscopic and bioptic findings of interstitial cystitis if a significant symptomatology was present. Patients should be willing and able to complete the necessary questionnaires.

The following patients were excluded from participating in this study: patients with tran-

sitional cell carcinoma of the bladder or other significant malignancy, pregnant or lactating, suffering from significant bacteriuria, diagnosis of hematuria, neurogenic bladder, indwelling catheters, chronic bacterial prostatitis, currently receiving or having received investigational drugs ≤30 days before screening, currently receiving or having had prior therapy with intravesical treatment (e.g. Uracyst, Cystistat®, heparin or Bacillus Calmette-Guérin (BCG)), receiving therapy for <3 months with antidepressants, anti-histaminics, hormonal agonists or antagonists; hence patient not stabilized on therapy (stable therapy defined as continuous treatment for ≥3 months), IC symptoms relieved by antimicrobials, anticholinergics or antispasmodics, functional bladder capacity of >400mL, neurologic disease affecting bladder function; any previous surgery or procedure having affected bladder function, current diagnosis of chemical, tuberculous or radiation cystitis, bladder or lower ureteral calculi, history of cancer within the last 5 years other than adequately treated non-melanoma skin cancers, active sexual transmitted disease, current vaginitis, endometriosis, any condition/disease which in the opinion of the investigator could interfere with patient compliance and/or interfere with the interpretation of the treatment results.

All patients gave written informed consent. Drop-outs and lost to follow-up are imputed as failures. Appropriate ethical approval was obtained according to national and international guidelines.

No compensation for the study was received by the patient, but the expense of the medical treatment and the medical consultations were free.

Intervention

Patients were single-blind randomized to receive one intravesical instillation of 2.0% sterile solution of sodium chondroïtin sulfate (Uracyst™) or DMSO 50% once weekly for 6 weeks. Uracyst™ is delivered as a 2% sterile solution in 20mL vials. DMSO is prepared as a 50% solution in 50mL physiologic serum. The bladder instillation was performed by a trained medical professional. Using a temporary catheter, the bladder is filled with CS 2% or DMSO 50%. The patients were asked to retain the solution in their bladder for at least 15-30 minutes to allow it to work, and then urinate normally.

No antibiotic therapy was administered to the patient, but the catheterization technique was absolutely sterile. Eventual necessity of post-instillation antibiotic therapy was decided on personal decision of the doctor.

Our standard instillation schedule is: one instillation every week for 6 weeks, one instillation every month for 4 months, one instillation every 2 months for 6 months, one instillation every 3 months, if possible, for maintenance.

Outcome assessment and study endpoints

Before and after treatment (at 7, 10 and 18 weeks), all patients were asked to fill in several questionnaires: the Interstitial Cystitis Symptom Index (4 questions) and Problem Index (4 questions) (ICSI/ICPI) (19) the Global Response Assessment (GRA) scale, the visual analog scale (VAS) for suprapubic pain, the 3-daily voiding diary, daily urinary frequency and nocturia. Each question in the O'Leary-Sant questionnaire was scored by the patient. Higher scores in each domain indicate greater symptom severity and impact on daily life. Maximum Symptom and Problem Index scores were 20 and 16, respectively (19). The GRA measures the overall improvement with therapy. The assessment asks: "As compared to when you started the current study (treatment), how would you rate your overall bladder symptoms now?". The patient was provided with the following seven response options: markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved and markedly improved. The VAS ranges from zero to 10 with zero representing no pain and 10 maximal pain. According to the study protocol the patients underwent 10 medical visits at weekly intervals for the first two months, thereafter at longer intervals. Table-1 presents the study overview.

The primary outcome measure was the difference of the percentage of patients who achieved score 6 or 7 on the Global Response Assessment (GRA) scale comparing the patient's present status with the pre-intervention status. A score of 6 indicates moderate improvement, while score 7

Table 1 - Study overview.

	Baseline	R/1	R/2	R/3	R/4	R/5	R/6	Q1	Q2	Q3
Week		1	2	3	4	5	6	7	10	18
VAS	x	x	x	x	x	x	x	x	x	x
Micturition diary	x							x	x	x
GRA								x	x	x
O'Leary-Sant	x							x	x	x
Instillation		x	x	x	x	x	x			
Adverse events		x	x	x	x	x	x	x	x	x

denotes marked improvement. Secondary parameters were the mean 24 hours frequency, nocturia episodes and functional bladder capacity measured on a 3-day micturition dairy, changes from baseline in the O'Leary-Sant questionnaire score and the assessment of suprapubic pain by the VAS.

Safety was assessed by monitoring adverse events at each visit. This publication shows a planned interim analysis for safety. A clinical evaluation committee evaluated the interim findings.

Statistical analysis

An intention-to-treat analysis was performed. Statistical analysis of the patient questionnaire data was performed using Med Calc version 8.1 (Belgium) Statistical analyses were considered significant at a p-value less than 0.05.

RESULTS

The analysis included 22 patients of both sexes (19 women and 3 men) treated with chondroïtin sulphate 2% and 14 (12 women and 2 men) treated with DMSO 50%. Baseline patient characteristics are presented in Table-2. The outcomes are shown in Table-3. For the primary outcome at 12 weeks, 72.7% of patients in the CS group achieved a GRA score of 6 or 7 compared with 14% of patients in the DMSO group (P=0.002, 95% CI 0.05-0.72). Decreases in pain (VAS), O'Leary-Sant nocturia and pain score compared to baseline were observed in both treatment groups and were statistically significant in the CS group. Although changes showed no statistically significant difference the CS group had a slightly smaller decrease in O'Leary-Sant IC total score (-7.2

Table 2 - Baseline patient characteristics.

O'leary sant questionnaire score	All patients	Dmso group	Chondroitin group	
Urgency	3.9 ± 1.9	3.7 ± 2.0	3.8 ± 2.0	ns
Void within 2h	5.1 ± 1.5	5.0 ± 1.7	5.2 ± 1.4	ns
Nocturia	4.6 ± 1.5	4.7 ± 1.5	4.6 ± 1.4	ns
Pain and burning	4.7 ± 1.6	4.3 ± 1.7	4.7 ± 1.6	ns
VAS Pain	6.3 ± 2.3	6.2 ± 2.3	6.4 ± 2.3	ns
VAS urgency	7.5 ± 1.5	7.3 ± 1.5	7.7 ± 1.4	ns
Total score	**29.4 ± 10.8**	**29.8 ± 11.8**	**21.5 ± 16.0**	**ns**

Table 3 - Drop-outs, Global Response Assessment, parameter changes vs. baseline.

	DMSO group	Chondroitin sulphate group
Drop-outs	8/14 (57%)	6/22 (27%)
GRA score 6 or 7	14.0%	72.7%
VAS reduction	8.3%	20%*
O'Leary total reduction	- 9.8 points	- 7.2 points
O'Leary nocturia subscale	4.7 to 4.0 (-0.7)	4.5 to 2.9 (-1.6)*
O'Leary pain subscale	4.3 to 3.7 (-0.6)	5.0 to 3.8 (-1.2)*

* statistically significant

points) compared to the DMSO group (-9.8 points). More than 50% of the patients in the DMSO group dropped-out (57%). The main reasons for treatment withdrawal in the DMSO group was the occurrence of side effects. Several patients reported pain during and after instillation, lack of efficacy, and intolerable garlic odor. Pain while holding DMSO in the bladder disappeared after voiding. By contrast, the drop-out rate in the CS group was only 27%. The main reasons were lack of efficacy or side effects. CS instillation side effects were all classified as Clavien-Dindo 1: urinary tract infection (n=2), urethral pain (n=2), dysuria (n=3).

Of the 16 patients who completed the CS treatment, all of them continued such treatment. We could not identify an ideal maintenance treatment schedule, as all patients received instillation cycles at different time intervals, according to the severity and recurrence of symptoms.

DISCUSSION

Several intravesical drugs have been studied in the past, including heparin, lidocaine, pentosan polysulphate sodium, dimethyl sulfoxide (DMSO), chondroïtin sulphate (CS), hyaluronic acid (HA) (and combination with CS), as well as investigational drugs such as GM-0111. Recently, intravesical administration of botulinum toxin (BTX) has been studied in patients with PBS/IC (20).

A number of uncontrolled, open-label clinical studies have suggested that intravesical CS may have benefit in some PBS/IC patients with no significant safety issues (12, 21, 22). Steinhoff et al. (2003) showed beneficial effects of CS treatment in patients who have positive potassium stimulation test (PST) results (22). Daha et al. (2008) demonstrated that in patients who respond symptomatically to increased GAG substitution therapy, cystometric bladder capacity is increased, whereas non-responders experience a decrease in bladder capacity (7).

A previously published, prospective, but uncontrolled, multicenter, real-life clinical practice study suggested that intravesical CS 2% may have an important role in the treatment of IC. The study showed a response rate of 47% at 6 weeks, which increased with additional monthly treatment sessions to 60% at 24 weeks. In all, 48 of 53 patients (90.6%) had a positive PST. There were no significant safety issues during the study (11).

Two previously published, randomized, placebo controlled studies reported clinical benefit but failed to show statistically significant differences in improvement for 20mL weekly instillations of CS 2% after 6 and 8 weeks, respectively (16, 17).

Recently, individual participant data from an open-label study (OLS) (11) and 2 small randomized placebo controlled studies (RCTs) (16, 17) assessing intravesical CS 2% in PBS/IC were pooled (similar inclusion/exclusion criteria, treatment and outcome assessment). This meta-analysis including 213 patients confirms that CS does indeed provide significantly more benefit than placebo. At the end of treatment period (week 10 for OLS,

week 7 for RCT1 and week 11 for RCT2), the overall GRA response rates were 43.2% (95% CI: 35.0, 51.5) and 27.4% (95% CI: 17.6, 37.2) for the CS and placebo groups, respectively. Pooled RR was 1.55 (P=0.014, 95% CI: 1.09, 2.22). The chance of having response to treatment was 55% significantly higher in the CS group than in the placebo group. The small decrease in total ICSI score and daily urine frequency between the two groups was less impressive (-0.8 and-0.5 points respectively) and not statistically significant. This underlines the importance of choosing the right patient for this treatment (23).

DMSO is approved in the U.S.A. as a standard therapy for intravesical treatment for PBS/IC. This is based on a small and old (1987) crossover study including 33 patients. Four intravesical treatments of 50mL 50% DMSO were administered at two-week intervals with 15 minutes retention. Patients were evaluated at one month post-treatment. When assessed subjectively, 53% of DMSO treated patients were markedly improved compared to 18% of the placebo treated patients. When assessed objectively (urodynamic assessment), 93% of the DMSO group and 35% of the placebo group were improved. No significant side effects to DMSO were noted (9). A further study conducted in 2000 by Peeker et al. demonstrated the superiority of instillations of DMSO over BCG in the reduction of pain and urinary frequency, but not of maximal functional capacity (24). The same studies are cited by a Cochraine review and by a NICE advice (25, 26). The recently AUA updated guidelines (2014) suggest limiting instillation dwell time to 15-20 minutes. DMSO is quickly absorbed into the bladder wall and longer periods of retaining are associated with significant pain. Side-effects include a garlic-like body odor in some people. This bothersome but relatively insignificant side effect may last up to 7 hours after treatment (27). Considering also a more recent study based on 28 patient that shows common side effects (48% of all the population) even using DMSO once a week for a 15-20 minute instillation (28), AUA guidelines suggest a prudent and controlled DMSO use (evidence-strength: grade C). In a recent work, Tomoe demonstrated that the population of patients with IC/BPS that mostly benefit from DMSO therapy is that with ulcerative Hunner lesions (29).

Our study is the first study in the literature comparing DMSO and CS for treatment of PBS/IC. The interim analysis of this study showed that CS 2.0% performed better than DMSO 50% in pain reduction and nocturia and in subjective outcome. CS 2.0% was also better tolerated than DMSO. Our data agree with those of a Downey et al. recent study, that found that intravesical CS reduced pain, urgency and O'Leary-Sant symptom and problem scores in patients with IC/PBS. All patients tolerated the treatment and no side effects were reported; a response to treatment was noted in patients who had failed a different intravesical bladder therapy (DMSO) (30). Both studies support the EAU guidelines recent update that do not recommend the standard DMSO use. We did not use a combined preparation of DMSO and lidocaine, to better identify the real direct benefit from DMSO without a possible confounding effect given by a simultaneous lidocaine instillation.

All patients had been adequately counselled and were aware about the possible incidence of side effects. Due to the high number of drop-outs in the DMSO arm caused by the high incidence of severe DMSO side effects, the clinical evaluation committee proposed to stop the study enrolment. Patients suffering of IC/BPS often complain of severe pain and urinary symptoms and come to medical attention to have effective and prompt treatments. It is not easy to achieve their full collaboration in a clinical trial and often do not accept the idea of a random assignment to a treatment option, requiring only the most effective. Patients were enrolled in this study during outpatient evaluation according to medical indication and patient desires. However, we can state that between 40% and 50% of patients declined enrollment because they wanted to choose the treatment and not accepting a random allocation.

Garlic odor is a typical feature of DMSO: patients were aware of this peculiar characteristic, but were blindly allocated to one of the two arms and never received confirmation by medical staff about the treatment they were receiving. Patient complaints were related more to side effects (pain and dysuria) than to the garlic odor.

Our results lead us to the conclusion that CS appears to be superior to DMSO in terms of efficacy and tolerability.

The limitations of this study are mainly the small sample size, the short follow-up and the lack of a placebo control group. On the other hand, randomization of patients to a placebo group may be difficult as PBS/IC patients were in severe pain and desperate for treatment. We did not do a washout period and then a crossover from one treatment to the other, this could represent a future implementation for this study.

To date, we have failed to stratify patients according to clinical phenotype because of the lack of proper biomarkers to categorize patients into groups that might respond differently to different interventions. A better approach for selecting patients with bladder-specific clinical phenotype might improve the overall response to intravesical CS 2% treatment (31).

CONCLUSIONS

Intravesical chondroïtin sulphate 2% (Uracyst™) is a viable treatment for patients with PBS/IC with minimal side effects. DMSO, while being considered the gold standard should be used with caution and with active monitoring of side effects. Further large-scale prospective RCTs with long-term follow-up are needed to determine the long-term efficacy and durability of CS 2%.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Female sexual function following a novel transobturator sling procedure without paraurethral dissection (modified–TOT)

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ABSTRACT

Purpose: To determine whether there is a difference in sexual function after modified and classical TOT procedures.
Materials and Methods: Of the 80 sexually active women with SUI, 36 underwent an original outside-in TOT as described by Delorme, and 44 underwent modified TOT procedure, between 2011 and 2015. The severity of incontinence and sexual function were evaluated using International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) and Female Sexual Function Index (FSFI) questionnaires preoperatively and 3 months after surgery.
Results: The postoperative ICIQ-SF score was significantly lower than the preoperative ICIQ-SF score in both groups (p=0.004 for modified TOT and p=0.002 for classical TOT). There was no significant difference in the ICIQ-SF score reduction between the two groups (14.1±2.1 vs. 14.4±1.9; p=0.892). Complication rates according to the Clavien-Dindo classification were also similar in both groups.
In both groups, difference between preoperative and postoperative FSFI scores revealed a statistically significant improvement in all domains.
Comparison of postoperative 3-month FSFI scores of modified and classical TOT groups showed statistically significant differences in arousal, lubrication and orgasm domains. Desire, satisfaction, pain and total FSFI scores did not differ significantly between two groups.
Conclusion: The modified TOT technique is a simple, reliable and minimal invasive procedure. The cure rate of incontinence and complication rates are the same as those of the classical TOT technique. However, due to the positive effects of minimal tissue damage on sexual arousal and orgasmic function, modified TOT has an advantage over the classical TOT.

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INTRODUCTION

Stress urinary incontinence (SUI) is extensively accepted as a social problem and defined as the involuntary leakage of urine with effort (1). Generally, causes of incontinence are hypermobility due to the loss of urethral support and lower pressure transmission to the urethra, compared to the urinary bladder (2). In the last decade, mid--urethral sling surgery has become the standard procedure for treatment of SUI in women. These procedures, including transobturator tape (TOT), tension-free vaginal tape (TVT), tension-free vaginal tape-obturator (TVT-O), and single incision sling (SIS), lead to less complications with comparable results to conventional open surgeries (3-5). To reduce the complications of retropubic sling procedure, transobturator approach was described

by Delorme in 2001 (5). In spite of the high volume of reports addressing the safety and efficacy of TOT, we believe that this technique can be further improved. In support of this, Onuk et al. have described a new technique without paraurethral dissection, which is called modified TOT (mTOT).

Incontinence-related sexual dysfunction resulting from decreased libido, recurrence dermatitis induced dyspareunia and fear of coital leakage has been reported by women (6). Even though some studies have found improvement on sexual function after mid-urethral sling procedures, there are also reports on negative effects (7-9). Different sling insertion techniques and the experience of the surgeon may lead to varying outcomes. Due to the G-spot (an erogenous area in some women) located on the anterior wall of the human vagina, extensive vaginal incision and paraurethral dissection in the sling procedure can affect sexual function (10).

The aim of our study was to evaluate sexual function prospectively in women before and after surgery for SUI, and to determine whether there was a difference in sexual function between classical TOT and modified TOT procedures using Female Sexual Function Index (FSFI) questionnaire.

MATERIALS AND METHODS

Sexually active women with stress urinary incontinence who underwent suburethral sling procedure between July 2011 and September 2015 were recruited to the prospectively planned study after receiving approval of the local ethical committee. Exclusion criteria were history of incontinence or pelvic reconstructive surgery, known psychiatric and neurological disorders, physical examination findings of above grade 1 pelvic organ prolapse. Of the 80 patients providing written informed consent, 36 underwent an original outside-in TOT as described by Delorme (5) and 44 underwent modified TOT procedure as described below. The preoperative evaluation included general history, physical examination, urine analyses, voiding dairy, urine culture and antibiogram, Marshall-Boney test, urethral Q-type test, urinary ultrasonography (to determine the amount of post voiding residue), and urodynamic evaluation (in mixed incontinence patients). The severity of urinary incontinence and its impact on quality of life (QoL) and sexual function were evaluated using International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) and Female Sexual Function Index (FSFI) questionnaires preoperatively and 3 months after the surgery. The FSFI is a 19-item questionnaire that allow investigation of six domains; sexual desire (items 1, 2), arousal (items 3-6), lubrication (items 7-10), orgasm (items 11-13), satisfaction (items 14-16) and pain during sexual intercourse (items 17-19) (11). Total FSFI score range was 2-36.

Surgical Procedure

The surgical area was sterilized and a Foley catheter was inserted in the lithotomy position. After the labial retraction sutures were placed, weighted vaginal speculum was inserted into the vagina. In alignment with the clitoris, 0.5cm bilateral groin incisions are made to the inferior of adductor longus muscle at the genitocrural fold level. After the helical needles were inserted the groin incisions, internal rotation through the obturator membrane was performed. Inferior ischiopubic ramus and obturator internus muscles were identified using the index finger of the opposite hand, without performing a vaginal incision. Subsequently, the needles were traversed through the obturator membrane, obturator internus muscle, periurethral endopelvic fascia and were felt under the vaginal mucosa with the index finger. During this process, anterior vaginal wall damage was not observed. In the next step, the needle was pushed until it reached 1.5cm below the urethral meatus (Figure-1). The same procedure was conducted for the opposite side as well, so that the needles met 1.5cm below the urethral meatus (Figure-2 and Figure-3), where a 0.5cm cut was made, and needle points were taken outside (Figure-4). The synthetic mesh was attached to the tips of the needles and the needles were backed out, bringing the mesh out through the level of the skin in the groin region. To arrange the tension of the mesh, a surgical clamp was placed between the mesh and the urethra. Incisions were closed with absorbable sutures.

Figure 1 - The needle is pushed until it reaches 1.5cm below the urethral meatus (left).

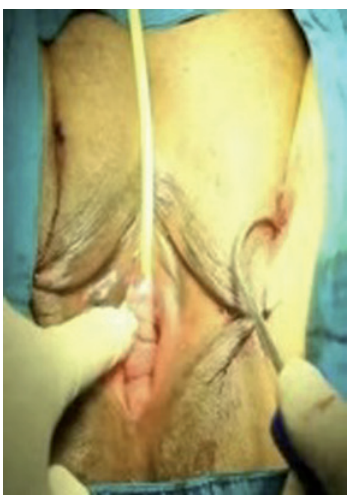


Figure 2 - The needle is pushed until it reaches 1.5cm below the urethral meatus (right).

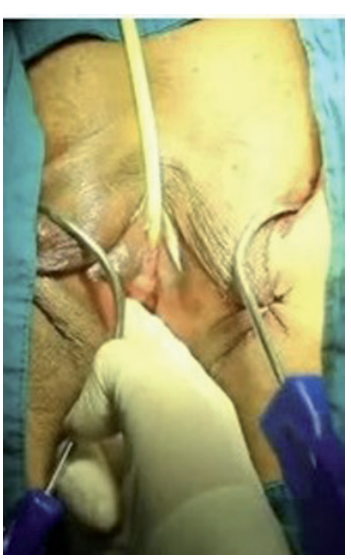


Figure 3 - The needles meet 1.5cm below the urethral meatus.

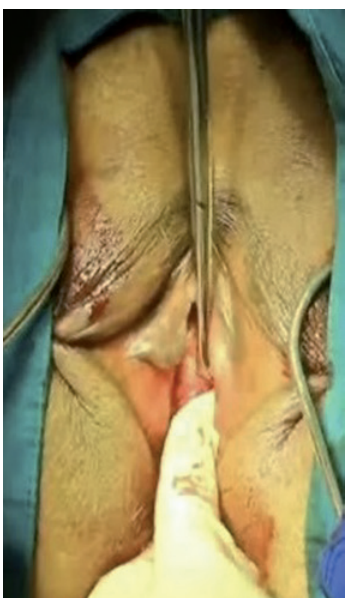
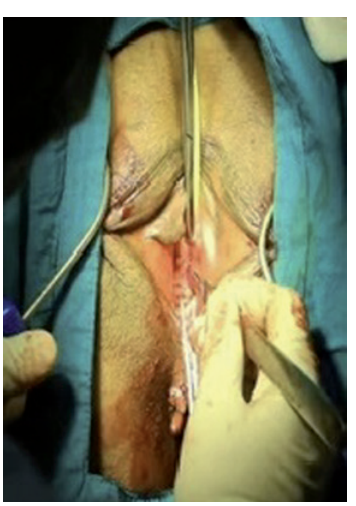


Figure 4 - A 0.5cm cut is made, and needle points are taken outside.



Cystourethroscopy was performed for the first 20 patients who underwent the modified technique. However, cystourethroscopy was later removed from the routine procedure since no injury was observed. Vaginal tampons were used for the classical technique group to control bleeding, but not for the modified technique group. Foley catheters of both groups were removed on the first postoperative day, as well as the vaginal tampons. All patients were discharged on the first postoperative day. Patients were allowed to engage in sexual intercourse after the fourth

postoperative week if they underwent original outside-in TOT, and tenth postoperative day if they underwent modified TOT due to better local (vaginal) conditions.

Statistical analysis

This study hypothesized that modified TOT procedure will be superior to the classical TOT in terms of postoperative sexual function. A total of 72 patients were required to achieve 80% power with a two-sided type 1 error of 0.05. Statistical analyses were performed using SPSS 21.0 (Chicago, Illinois) and $p<0.05$ was considered statistically significant. Categorical variables were analyzed using Chi-square or Fisher's exact tests, and continuous variables were analyzed using Mann-Whitney U and Kruskal-Wallis tests.

RESULTS

Patient characteristics for modified TOT and classical TOT groups are shown in Table-1. There were no statistical differences between the two groups in terms of age, BMI, parity, menopausal, degree of education, diabetes, hypertension, smoking, frequency of intercourse and medical treatment for SUI.

The mean postoperative ICIQ-SF score was significantly lower than the preoperative ICIQ-SF score in both groups (16.6 vs. 2.5; p=0.004 for modified TOT and 17.5 vs. 3.1; p=0.002 for classical TOT). There was no significant difference in the ICIQ-SF score reduction between the two groups (14.1±2.1 vs. 14.4±1.9; p=0.892). Complication rates according to the Clavien-Dindo classification were also statistically similar in both groups (Table-2).

In both groups, preoperative and postoperative FSFI scores revealed significant improvements in all domains (desire, arousal, lubrication, orgasm, satisfaction, pain and total score) (Table-3).

Comparison of postoperative FSFI scores between modified TOT and classical TOT procedures showed statistically significant differences in arousal, lubrication and orgasm domains (Table-4). Desire, satisfaction, pain and total FSFI scores did not differ significantly between two groups (Table-4).

Table 1 - Comparison of baseline characteristics of patients.

	Modified TOT n=44	Classical TOT n=36	p value
Age, years	54 (32-67)	52 (36-67)	0.215
Body mass index, kg/m^2	32 (22-41)	31 (24-40)	0.554
Parity, n	3 (0-6)	3 (2-6)	0.116
Menopausal, n (%)	31 (70.4%)	26 (72.0%)	0.862
Degree of education			0.941
No education	6 (13.7%)	4 (11.1%)	
≤ High school	30 (68.2%)	25 (69.4%)	
University	8 (18.1%)	7 (19.5%)	
Diabetes, n (%)	14 (31.8%)	11 (30.5%)	0.904
Hypertension, n (%)	16 (36.3%)	12 (33.3%)	0.777
Smoking, n (%)	7 (15.9%)	6 (16.6%)	0.927
Frequency of intercourse			0.882
>2/week	5 (11.3%)	5 (13.8%)	
1-2/week	28 (63.6%)	21 (58.4%)	
1-3/month	11 (25.1%)	10 (27.8%)	
Treatment (SNRI) for SUI, n (%)	17 (38.6%)	13 (36.1%)	0.816

Table 2 - Complications reported according to the Clavien-Dindo classification.

	Modified TOT	Classical TOT	p value
Grade I	2 (4.5%)	3 (8.3%)	
Dyspareunia	2	3	0.662
Grade II	6 (13.6%)	7 (19.4%)	
Inguinal pain	2	4	0.401
Urgency	2	3	0.653
Vaginal damage	2	0	0.499
Grade IIIa	1 (2.2%)	2 (5.5%)	
Urinary retention	1	2	0.585

DISCUSSION

Female sexual dysfunction is a major health problem associated with age, degree of education, medical and psychosocial situations, and is composed of orgasmic disorder, dyspareunia and lack of sexual desire (12). Epidemiological studies have demonstrated that approximately 40% of women have sexual problems worldwide (13). It is well known that the prevalence of sexual dysfunction in women with stress urinary incontinence is higher than healthy continent females (14). However, there are conflicting results concerning the effect of incontinence surgery on sexual function (8-10). Pastore et al. used FSFI questionnaire to evaluate sexual function in 48 women who underwent TVT-O and SIS procedures. The postoperative FSFI scores were reported to improve significantly ($p<0.001$) in both groups, with high rate of continence (15). Naumann et al. assessed sexual function six months after TVT and SIS surgeries and reported that, in comparison to preoperative scores, all postoperative domain scores and total FSFI score increased significantly in both surgical groups (16). Results of Simsek et al. and Abo El--Enen et al. also indicate an improvement in FSFI scores after the amelioration of incontinence using transobturator sling procedure (14, 17). In contrast, a meta-analysis of eighteen studies showed that sling surgery had negative impacts on 13.1% of patients and there was no change in symptoms for 55.5% (18). In our study, FSFI scores showed statistically significant improvements in all domains in the 3-month follow-up. We believed that sexual dysfunction in women with urinary leakage has a psychological background, and achieving continence during sexual intercourse may improve self-confidence and sexual performance.

There are numerous studies in the literature that compare postoperative sexual function of four minimal invasive surgical techniques; TOT, TVT, TVT-O and SIS. Elzevier et al. evaluated postoperative sexual complaints of 77 patients who underwent TVT-O and TOT for SUI. Jang et al. also evaluated the possible effects of two operative methods on sexual function, including retropubic route and transobturator route. FSFI scores of forty-seven patients were analyzed. In both comparative studies no difference were observed except pain during intercourse after the TOT procedure. Although the exact cause is not clear, pain disorder in the TOT group may be related to vaginal injury and narrowing, vascular or neuronal detriment (19, 20). On the other hand, the first prospective comparative study in the literature that analyzed TVT and SIS reported, no difference between postoperative pain scores for the two surgical techniques. Interestingly, a statistical difference was found for lubrication and orgasm domains, in favor of the TVT procedure (16). In another comparative study conducted by Murphy et al., 329 patients were treated with

Table 3 - Changes between preoperative and postoperative scores on the FSFI.

	Modified TOT			Classical TOT		
	Preoperative	Postoperative	p value	Preoperative	Postoperative	p value
Desire	3.06±0.76	3.72±0.82	<0.001	3.13±0.72	3.69±0.92	<0.001
Arousal	3.53±0.96	4.52±1.02	<0.001	3.46±0.88	4.09±0.95	<0.001
Lubrication	4.36±1.12	4.97±1.41	<0.05	4.11±1.22	4.52±1.16	<0.05
Orgasm	3.96±1.01	4.82±1.36	<0.001	4.02±1.87	4.46±0.94	<0.001
Satisfaction	4.56±0.99	5.42±1.10	<0.001	4.42±0.88	5.12±1.11	<0.05
Pain	4.12±0.78	5.21±1.34	<0.001	4.22±0.96	4.92±1.18	<0.05
Total	**23.59±4.12**	**28.66±5.95**	**<0.001**	**23.36±4.13**	**26.80±4.97**	**<0.001**

Table 4 - Comparison of postoperative FSFI scores for modified and classical TOT.

	Modified TOT	Classical TOT	p value
Desire	3.72±0.82	3.69±0.92	0.644
Arousal	4.52±1.02	4.09±0.95	<0.05
Lubrication	4.97±1.41	4.52±1.16	<0.05
Orgasm	4.82±1.36	4.46±0.94	<0.05
Satisfaction	5.42±1.10	5.12±1.11	0.168
Pain	5.21±1.34	4.92±1.18	0.619
Total	**28.66±5.95**	**26.80±4.97**	**0.328**

TVT or TVT-O procedures. Preoperative and postoperative sexual functions were evaluated with The Pelvic Organ Prolapse/Incontinence Impact Questionnaire (PISQ-12). The two groups did not differ significantly in terms of sexual function (21). In our study, improvement in arousal (4.52 vs. 4.09; $p<0.05$), lubrication (4.97 s 4.52; $p<0.05$) and orgasm (4.82 vs. 4.46;$p<0.05$) domains were significantly higher in the m-TOT group than the classical TOT group. Additionally, total FSFI score improvement was higher in women with m-TOT, but this difference was not statistically significant. (28.66±5.95 vs. 26.80±4.97; $p=0.328$). In the beginning of our study, we hypothesized that, in comparison to the classical TOT, a surgical approach without wide vaginal incision and paraurethral dissection would result in less postoperative pain, earlier sexual intercourse and improved sexual function. As known, extensive anterior vaginal wall incision and paraurethral dissection may impair the neurovascular tissues, induce vaginal scarring and lead to orgasmic and arousal problems (22, 23). In concordance with literature, our findings revealed that m-TOT technique has an advantage on vaginal fibrosis, preserving innervation and enhancing the orgasmic/arousal function. To resume sexual activity earlier due to the lack of introital wound tenderness is another gain of our technique.

CONCLUSIONS

The modified TOT technique is a simple, reliable and minimal invasive procedure. The cure rate of urinary incontinence and complication rates are the same as the classical TOT technique. However, due to the positive effects of minimal tissue damage on sexual arousal and orgasmic function, modified TOT has an advantage over the classical TOT. Sexual function assessment was limited to three months after the surgery and this was the partial limitation or our study. Additional studies providing longer-term follow-up reports may improve our insight about the effects of modified TOT procedure.

CONFLICT OF INTEREST

None declared.

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Artificial urinary sphincter for urinary incontinence after radical prostatectomy: a historical cohort from 2004 to 2015

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ABSTRACT

This study aimed to retrospectively evaluate a cohort of patients with prostate cancer and persistent urinary incontinence after radical prostatectomy. From January 2004 to December 2015, eighty-six individuals were identified to have received an AUS implant, provided by a private nonprofit HMO operating in Belo Horizonte, Brazil. On total, there were 91 AUS implants, with a median interval between radical prostatectomy and AUS implant of 3.6 years (IQR 1.9 to 5.5). The rate of AUS cumulative survival, after a median follow-up of 4.1 years (IQR 1.7-7.2 years), was 44% (n=40). The median survival of AUS implants was 2.9 years (IQR 0.5-7.9 years). Thirty-seven AUS implants (40.7%) resulted in grade III surgical complications. There were 5 deaths at 2.1, 4.7, 5.7, 5.7 and 6.5 years of follow-up, but none due to causes directly associated to the AUS implant. Persistent severe incontinence was documented in 14 (15.3%) additional patients. From the 51 AUS implants which resulted in grade III surgical complications or persistent severe incontinence, 24 (47.1%) underwent surgical revisions. Explantation of the sphincter or its components was observed in 6 cases (25.0%). Mechanical failure, described as fluid loss and/or inability to recycle the AUS device, was observed in 4 devices (16.7%). In conclusion, although AUS implants are recommended as the gold-standard treatment of severe urinary incontinence after prostatectomy, the observed high rates of malfunction and grade III adverse events are a matter of concern warranting further assessment on the safety and efficacy of these devices.

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Urinary Incontinence; Prostatectomy; Prostatic Neoplasms; Urinary Sphincter, Artificial

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INTRODUCTION

Currently, prostate cancer is the leading type of cancer in men worldwide, with a global estimated incidence of 1.4 million cases a year (1). In spite of the risks of urinary incontinence, and other adverse events such as impotence, radical prostatectomy is still the most frequently performed treatment for this condition (2).

Urinary incontinence, the involuntary urethral loss of urine, can be caused by radical prostatectomy through a direct injury of the urethral sphincter or as a consequence of bladder denervation, resulting in bladder dysfunction such as detrusor overactivity (3). While a small amount of incontinence may not cause problems, larger degrees of incontinence can lead to major impact on a patient's quality of life (4). In these cases,

when incontinence persists despite conservative therapy, the implantation of an artificial urinary sphincter (AUS) may be recommended (5, 6).

An AUS consists of three silicone components: a cuff, a balloon reservoir, and a pump. Each of these components is attached to a length of silicone tubing and connected together during the surgical implant procedure (7). In spite of its known efficacy in the management of persistent urinary incontinence, studies have reported disastrous complications resulting in early device removal and an increased rate of surgical revisions (8-18). Therefore, this study aimed to retrospectively evaluate a series of cases of AUS implants in patients with persistent urinary incontinence after radical prostatectomy, at a private nonprofit health maintenance organization (HMO) in Brazil.

PATIENTS AND METHODS

This study consisted of a convenience sample of individuals with persistent urinary incontinence after radical prostatectomy performed to treat prostate cancer. We retrospectively collected data from individuals who had an AMS800® AUS device implanted from January 2004 to December 2015, while they were being provided healthcare assistance by a private nonprofit HMO operating in Belo Horizonte, Brazil. Data was collected from AUS implants performed in 15 different hospitals in the Belo Horizonte metropolitan region, the third largest metropolitan area of Brazil. Patients were excluded if they had a history of any urological surgical procedure other than radical prostatectomy.

The primary outcomes of this study were the assessment of grade III surgical complications following AUS implantation, which were defined, according to the Clavien-Dindo classification score, as any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure requiring surgical, endoscopic or radiological intervention (19, 20). The need for surgical revision was defined as the first repeat operation on the AUS, including due to total or partial explantation or to mechanical failure. Demographic information collected for each patient included age, date of the radical prostatectomy, history of previous radiotherapy, date of AUS implantation, costs, need for revision or removal of the device. Data was extracted from an administrative database, using the software Oracle Business Intelligence®.

After a descriptive analysis of the data, patients were divided in two groups, according to their history of radiotherapy. Continuous data were expressed as medians and interquartile range (IQR) or means and standard deviation (SD), when appropriate. Dichotomous variables were compared using two-sided Fisher's exact test. The level of significance was set at $p<0.05$. Kaplan-Meier estimates of survival curves were built using the software STATA 13.1 (Stata Corp, College Station, TX, USA).

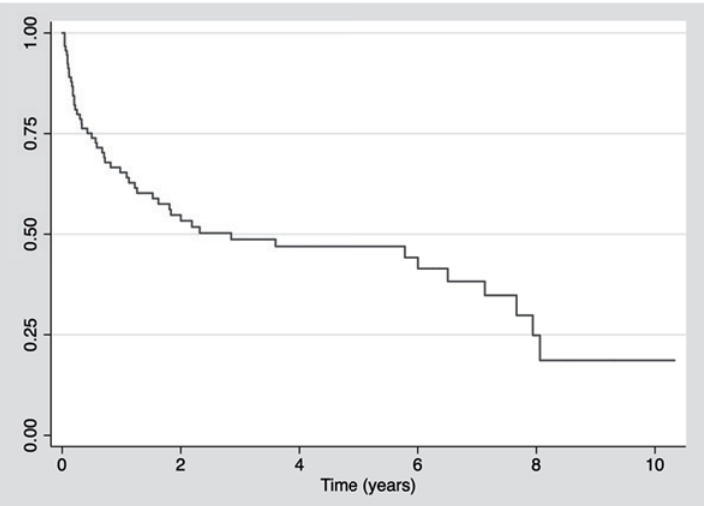
This historical cohort resulted in no interventions, neither during the course of the instituted treatment nor after the observed outcome. Privacy of subjects and the confidentiality of their personal information were handled in accordance to the ethical principles of the Declaration of Helsinki. This study was approved by the local ethics committee.

RESULTS

From January 2004 to December 2015, 86 men were identified to have received an AUS implant after radical prostatectomy. The mean age at the time of the AUS implantation was 69.5 years (range 47.5 to 86.0 years). Five patients (5.8%) underwent a second AUS implant, due to AUS malfunction, resulting in a total of 91 devices. Total device costs were estimated in roughly US$1.000.000.00 or US$11.628.00 per patient. Implants were performed in 15 different hospitals by 28 different surgeons. The median interval between radical prostatectomy and AUS implant was 3.6 years (IQR 1.9-5.5 years). The rate of AUS cumulative survival, after a median follow-up of 4.1 years (IQR 1.7-7.2 years), was 44% (n=40). The median survival of AUS implants was 2.9 years (IQR 0.5-7.9 years), as shown in Figure-1.

Thrity-seven AUS implants (40.7%) resulted in grade III surgical complications, distributed as follows: scrotal abscess (n=10, 11.0%); sepsis due to prosthesis infection (n=9; 9.9%);

Figure 1-Artificial urinary sphincter survival curve.



urethral fistula (n=7; 7.7%); urethral erosion (n=6; 6.6%); urethral stenosis (n=3; 3.3%); acute postoperative urinary retention (n=1; 1.1%); testicular torsion (n=1; 1.1%). Persistent severe incontinence was documented in 14 (15.3%) additional patients. There were 5 deaths at 2.1, 4.7, 5.7, 5.7 and 6.5 years of follow-up, but none due to causes directly associated to the AUS implants.

From the 51 AUS implants which resulted in grade III surgical complications or persistent severe incontinence, 24 (47.1%) demanded surgical revisions. The median time to first revision was 8.1 months (IQR 2.2-21.9 months). The revisions were triggered by: failure of the cuff (n=8; 33.3%); the need to replace the balloon reservoir (n=3; 12.5%); the need to install a second cuff (n=2; 8.3%) or to reposition of pumps (n=1; 4.2%). Explantation of the sphincter or its components was observed in 6 cases (25.0%). Mechanical failure, described as fluid loss and/or inability to recycle the AUS device, was observed in 4 devices (16.7%).

Twelve (14.0%) patients were exposed to radiotherapy (RT) before the implant of an AUS. There were no significant statistical differences for the rate of surgical complications (p=0.7) and the need for surgical revisions (p=0.6) after patient stratification according to their history of prior RT (Table-1).

Table-1 - Frequency of surgical revisions and grade III surgical complications after AUS implantation according to the history of previous radiotherapy

	Previous radiotherapy (n=12)	No previous radiotherapy (n=74)	P*
Presence of grade III surgical complications - n(%)	4 (33%)	33 (44%)	0.7
Underwent surgical revision - n(%)	2 (16%)	22 (30%)	0.6

*Two-sided Fisher's exact test.

DISCUSSION

Therapeutic strategies for urinary incontinence after prostatectomy include conservative treatment and pharmacotherapy (21, 22). For those who have persistent severe urinary incontinence in spite of these measures, surgical options, such as the use of transurethral bulking agents, perineal slings or AUS implants, are usually recommended. Currently, AUS implants are considered the gold standard surgical option (23, 24). Nevertheless, studies evaluating AUS efficacy and long term complications are scarce, especially in low and middle-income countries, such as Brazil.

In this context, this study retrospectively evaluated a cohort of patients with persistent urinary incontinence after radical prostatectomy that underwent AUS implantation. In our cohort, the rate of AUS cumulative survival, after a median follow-up of 4.1 years, was 44.0% (n=40). Thirty-seven AUS implants resulted in grade III surgical complications, while fourteen resulted in persistent severe incontinence. Our median time to first revision was 8.1 months (IQR 2.2-21.9 months) and the rate of surgical revision was 26.4% (n=24). When compared to our cohort, Ravier et al. (18), reported a longer median time to first revision (11.7 months), with a similar rate of surgical revisions (31.0%). In that cohort, with 122 patients, there were no revisions due to mechanical failure of the device, differently from what was observed in 4 of our patients.

Ravier et al. (18) reported an overall rate of continence of 68.9%. Other studies reported a long-term complete continence of only 20.0% (14) and surgical revision rates of 22.0% (10) and 25.0% (25). In similarity to our results, in 2012 Wang et al. (15) reported, after a median follow--up of 52 months (4.3 years), the need for at least one intervention in 53.0% of his sample. Revisions occurred after a median time of 20.1 months and were most commonly motivated by recurrent incontinence (56.7%), mechanical malfunction (22.0%) and infection or erosion (18.6%).

In the face of the high rates of AUS complications reported in the medical literature, some authors have tried to identify possible risk factors. In 2015, Hird et al. (16) published a study suggesting that despite the recent improvements in radiation treatment techniques and equipment, previous exposure to radiotherapy could still be considered a risk factor for surgical complications after AUS implants. In our study, complications were numerically more prevalent in patients without previous history of radiotherapy, however this observed difference was not statistically significant. Similar results were reported by Kim et al. (26), which also didn´t find significant differences in AUS complication rates according to previous RT exposure. In spite of these results, our findings should be analysed in the context of lack of power to address the impact of RT in this population since only 12 (14.0%) patients in our cohort were previously exposed to RT. Other limitations of the present study is its retrospective, non-randomized and uncontrolled design. Because of its nonconcurrent nature and its data source limited to an administrative database, we did not have access to clinical data, such as time between RT and AUS implantation, radiation dose or RT type. We also didn't have access to quality-of-life or functional parameters related to clinical outcomes of the AUS. Finally, in this study, 91 AUS implants were performed in 15 hospitals by 28 different surgeons, raising the question whether suboptimal surgical expertise might have influenced our results. In spite of these limitations, as far as we know, this is the first study to assess AUS implants in Brazil.

In conclusion, although AUS implants are recommended as the gold-standard treatment for severe persistent urinary incontinence after prostatectomy, the observed high rates of device malfunction and grade III surgical complications are a matter of concern warranting further assessment on the safety and efficacy of these devices.

CONFLICT OF INTEREST

None declared.

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One – staged reconstruction of bladder exstrophy in male patients: long – term follow-up outcomes

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ABSTRACT

Introduction: The surgical correction of bladder exstrophy remains challenging. In our institution, the repair has evolved from a staged repair to one-stage reconstruction. The one-stage reconstruction includes; bladder closure, Cantwell-Ransley neourethroplasty and abdominoplasty using groin flaps, without the need of pelvic ostheotomies. Repair of urinary continence (UC) and vesicoureteral reflux (VUR) is done after development of the infant.

Objective: To present our experience of our modified one-stage reconstruction of bladder exstrophy in male patients.

Materials and Methods: Medical records of male patients submitted to one-stage reconstruction of bladder exstrophy were analyzed retrospectively. Fifteen exstrophy bladder patients with mean age 4.2±7 years were treated at our institution between 1999-2013.

Results: Eleven patients were referred to us after previous surgery. Sixteen procedures were performed; one patient had complete wound dehiscence and needed another reconstruction (6.7%). Mean follow up was 10.3±4.5 years. No patient has had a loss of renal function. Postoperative complications: four patients (26.6%) presented small fistulas, one presented penile rotation. Eleven patients (73.3%) patients underwent bladder-neck surgery. Five (33.3%) required bladder augmentation. Three cases (20%) needed subsequent treatment of VUR.

At the time of our review nine (60%) patients achieved UC, two (13.3 %) patient without additional procedure. A mean of 3±1.1 procedures (2-5) was accomplished per children.

Conclusions: One-stage reconstruction minimizes the number of surgical procedures required to achieve UC and potentiates bladder-neck function. The advantages of using groin flaps over current techniques for complete repair are the small risk for penile tissue loss and the avoidance of ostheotomies.

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Bladder Exstrophy; Reconstructive Surgical Procedures; Male; Patients

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INTRODUCTION

Classic bladder exstrophy is a rare malformation of the genitourinary tract and its incidence is around 1 case to 30.000 to 40.000 live births (1). The surgical management of bladder exstrophy has evolved during the last years, with the standard treatment until the late 1950s being urinary diversion with ureterosigmoidostomy. Afterwards, in 1970s it evolved to a staged repair, with early

pelvic ring approximation and abdominal wall, bladder and posterior urethral closure performed as a first stage, followed by second stage neourethroplasty (modified Cantwell-Ransley technique) and finally a bladder neck surgical reinforcement such as Yong-Dees-Leadbetter procedure (2). The modern staged repair (MSRE) technique involves bladder closure shortly after birth, followed by epispadias repair at age 6-12 months and bladder neck reconstruction at age 4-5 years when it is thought that the child can cooperate with attempting continence.

In 1990s, Mitchell introduced the concept of one-stage reconstruction of extrophy, where all the aforementioned procedures were performed as a single surgery comprehensive approach (3). The concept of this approach was to decrease the number of surgical procedures required to achieve continence as well as achieve early bladder neck resistance and bladder cycling (4). This technique presented good results, although it has some drawbacks such as risk of penile tissue loss and necessity of ostheotomies in older children or after failed repair.

Placing the posterior urethra and bladder deep into the pelvis in combination with a tension-free closure and adequate postoperative management prevent complications and are now consensus among pediatric urologists (5). The two well-described techniques: MSRE (6) and one-stage reconstruction of bladder exstrophy advocates the observance of these fundamental principles (4).

In our institution, the repair of bladder exstrophy has evolved from a staged repair to one-stage reconstruction (Table-1). However, we describe our one-stage reconstruction of bladder exstrophy, performed in University of São Paulo, since late 1990s as a single comprehensive surgery that was adapted to our environment since it was common to receive older children with previous failed repairs. In this procedure, we perform bladder closure and positioned it deep in the pelvis, Cantwell-Ransley neourethroplasty and abdominoplasty using groin flaps, without the need of pelvic ostheotomies. Urinary continence (UC) and vesicoureteral reflux (VUR) are addressed later, at toilet training age.

OBJECTIVE

To present our experience of our modified one-stage reconstruction of bladder exstrophy in male patients.

MATERIALS AND METHODS

Medical records of male patients submitted to one-stage reconstruction of bladder exstrophy were analyzed retrospectively. Fifteen exstrophy bladder patients (16 procedures) with mean age 4.2±7 years (45 days to 22 years) were treated at our institution between September 1999 and

Table 1 - Treatment of bladder exstrophy in male patients (time table).

Before 1973	1973-1985	1982-2011	1999-2015
Incontinent Urinary Diversion	Colocystoplasty	Modern Staged Repair	One-Stage Reconstruction
	1. Cutaneous uretero colonic conduit	1. Bladder closure + abdominoplasty	1. Cystorrhaphy + cantwell-ramsley neourethroplasty + abdominoplasty using groin flaps
	2. Tubularization of the exstrophic bladder	2. Phalloplasty + urethroplasty	
	3. Colonostomy closure + proximally anastomosed to the tubularizated bladder	3. Bladder neck reconstruction (and ureteral reimplantation)	2. Bladder neck reconstruction at age 4 to 5 years (and ureteral reimplantation)
		4. Bladder augmentation if necessary	3. Bladder augmentation if necessary

October 2013. Nine patients were referred to us after previous failed bladder closure elsewhere. Additionally, five patients had undergone other surgical procedures: inguinal herniorrhaphy in two and urinary diversion in three cases (two colonic conduits, one bilateral cutaneous ureterostomy).

At time of bladder exstrophy repair, patients that were referred to us after previous failed bladder closure elsewhere had a mean age of 6.5 years (2 months to 22 years) and children without previous attempts of repair had a mean age of 9 months (6 to 18 months). At time of data analysis, the group with previous surgery had mean age of 17.7 years (6 to 34 yeas) and the naïve surgical group had a mean age of 9.5 years (3 to 18 years).

All patients were treated with cystorrhaphy, Cantwell-Ransley neourethroplasty, and abdominoplasty using groin flaps to close the abdominal wall defect, without osteotomies. Cystorrhaphy consists in bladder closure in two planes and placing the posterior urethra and bladder deep into the pelvis performing a tension-free closure of the bladder; bladder neck surgery was only performed at time of toilet training. Cantwell-Ransley neourethroplasty begins with extensive dissection of the epispadias but without complete penile disassembly providing easy access to the intersymphyseal ligament, which is deeply incised, dissection of each neurovascular bundle and the urethral plate with its spongiosal tissue, preserving the glans; then the urethral plate is tubularized as shown in Figure-1A. The corpora are rotated medially by approximately 90º and maintained in this new configuration by a proximal caverno-cavernostomy; this new anastomosis between the corpora keeps the urethra in its ventral position and gives the penis a dangling position when flaccid (Figure-1B).

Abdominal wall repair consists in using hypogastric skin and rectus abdominis and obliquus externus abdominis muscle aponeurosis flaps (these groin flaps are rotated to the midline resulting in a very strong abdominal wall). Groin flaps are made of the rectus anterior aponeuroses rotated medially, flipped over, and sutured with prolene sutures to close the defect (Figure-1C) (7). By rotating the facial flaps medially, complete reinforcement of the abdominal wall to the level of the pubic bone is achieved.

All received broad-spectrum intravenous antibiotics (3rd generation cephalosporins) intra-operatively and continued postoperatively (1st generation cephalosporin) and analgesics and anti-inflammatory drugs as needed for 1-2 weeks. A urethral catheter was left for 7-10 days and two plastic catheters were used for drainage of subcutaneous tissue (Figure-1D).

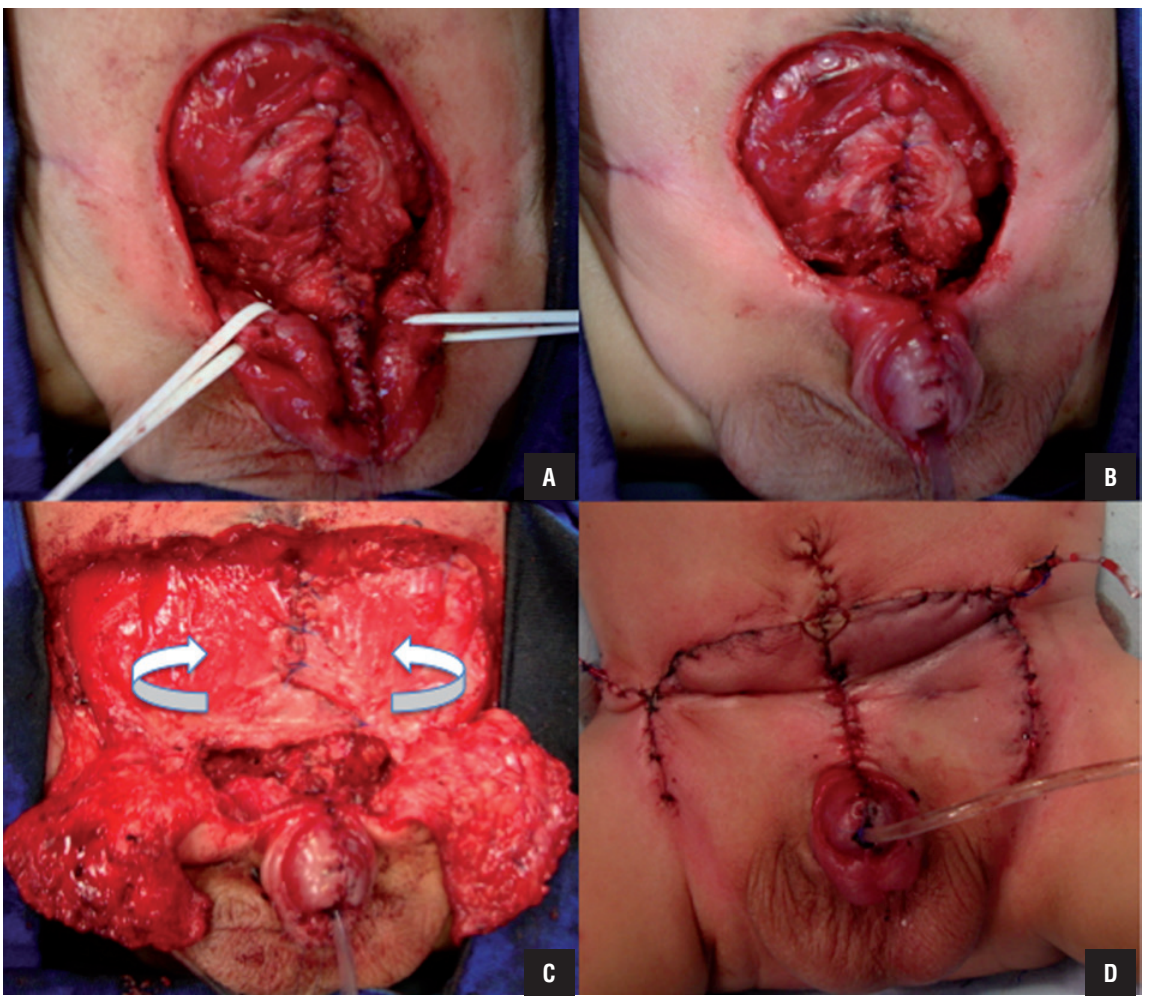
Successful primary closure was defined as an acceptable functional outcome with no wound dehiscence or fistula; failed closure was defined as wound dehiscence.

Considered variables were length of surgery, length of hospital stay, complications related to one-stage reconstruction and urinary continence.

Bladder neck reconstruction was performed at age 4 to 5 years when it is thought that the child can cooperate with attempting continence. Additional procedures were needed in many cases to achieve the treatment goals (urinary continence, normal genital cosmetic and preservation of upper urinary tract). Patients were considered continent if dry after the age of toilet training (3 to 5 years), and for those under this age, if dry for intervals between 2 to 3 hours. They were considered incontinent if any urinary leakage was observed between voiding or catheterizations from either the catheterizable channel or the urethra (for toilet trained children) or if they could not achieve continence intervals of ≥2 hours (for toddlers and infants). Patients who were using diapers were included in the incontinent group.

Regular clinic visits and periodic kidney, urinary tract and bladder ultrasonography were performed every 6 months to 1 year. Voiding cystourethrography was performed only in cases of urinary tract infections, upper urinary tract dilatation and/or urinary incontinence (small intervals with continuous dribbling for infants and toddlers). Urodynamics were performed in patients before bladder neck repair. Bladder cystometric capacity expected to age (BcapE) was determined by Koff's formula, [(age in years + 2) x 30] mL, for children over 2 years; (7 x body weight in kg) mL, for boys under 2 years old. Augmentation was indicated when bladder capacity was low and/or compliance was poor.

Figure 1 – Steps of one-stage reconstruction: A) Closure of the bladder and tubularized urethra; B) Penile closure; C) Groin flaps; D) Final aspect



RESULTS

Mean operative time was 325±61.3 minutes (240 to 420 min) and mean hospital stay was 13.2±5.8 days (6 to 23 days). Successful closure was achieved in 14 patients (93.3%) performing a single procedure; one patient had complete wound dehiscence and needed another reconstruction (6.7%) - this patient had previous bladder closure elsewhere. None had ischemic loss of the glans or corporal bodies. Other four patients (26.6%) presented small fistulas and one (6.7%) presented penile rotation as a complication related to one-stage reconstruction. Mean follow-up was 10.3±4.5 years (2y8mos to 16y).

Nine patients (60%) are continent at present: seven voids spontaneously and two are on clean intermittent catheterization. From the group with previous bladder closure elsewhere, five (55%) achieved continence and from the group of naive patients, four (66.7%) are continent. All patients have normal kidneys on US and normal serum creatinine. Seven patients (46.6%) showed vesicoureteral reflux on voiding cystourethrography performed after urinary tract infections.

Additional procedures were needed to achieve the treatment goals, including upper urinary tract protection, urinary continence and satisfactory cosmetic results. Eleven patients (73.3%) patients underwent bladder neck surgery

(nine pts. underwent Young Dees Leadbetter and two was submitted to bladder neck injection of Durasphere), and seven out of eleven achieved continence. Five (33.3%) required augmentation ileocystoplasty and Mitrofanoff stoma to facilitate CIC. There are two out of five patients with bladder augmentation that are still incontinent. VUR needed subsequent treatment in three cases (20%) (ureteral reimplantation). Three boys (20%) required inguinal herniorrhaphy during follow-up (two unilateral and one bilateral). A mean of 3±1.1 procedures (2-5) was accomplished per children. Six patients have still pending procedures (three awaits for augmentation cystoplasty associated with bladder neck reconstruction and three cases need urinary fistula repair) (Table-2).

Patients that were referred to us after previous failed bladder closure elsewhere needed more procedures then children without previous bladder closure, (mean of 3.3±1.1; mean of 2.5±0.8 procedures per children, respectively). The most common additional procedure was bladder neck surgery. Eight patients (88%) from the group with previous bladder closure performed elsewhere needed the procedure, while three patients (50%) from the naive treatment group needed this procedure. Moreover, at present, five out of nine (55%) patients with previous failed bladder closure are continent and four out of six

Table 2 - Patient characteristics and results of operation with one-stage reconstruction.

Treatment of naive patients						
AA	AR	OT(min)	CS	Aug	ARS	Results
3 years	1.5m	315				Continent (VS)
6 years	2m	310				Incontinent
7 years	4m	315				Incontinent
12 years	1.5m	330	+			Continent (VS)
14 years	10m	240	+	+		Continent (CIC)
15 years	6m	270	+			Continent (VS)
Previous bladder clousure elsewere						
AA	AR	OT(min)	CS	Aug	ARS	Results
7 years	1yr5m	405	+	+	+	Incontinent
11 years	8yr	420				Continent (VS)
12 years	3yr	300	+		+	Incontinent
15 years	11m	265	+	+		Incontinent
16 years	5m	390	+			Continent (VS)
16 years	7m	285	+			Incontinent
19 years	3yr	260	+	+	+	Continent (CIC)
30 years	21yr	350	+	+		Continent (VS)
34 years	22yr	420	+			Continent (VS)

AA = age at analysis; PBC = previous bladder closure; AR = Age at reconstruction; OT = Operative time; CS = Continence Surgery, Aug = augmentation; ARS = Anti-reflux surgery; CIC = clean intermittent catheterization; VS = voids spontaneously.

(67%) of those without previous bladder closure are continent.

DISCUSSION

The management of children with bladder exstrophy remains a challenge and despite the choice of approach (staged versus one-stage reconstruction), patients have to undergo several procedures in order to attain goals of surgical treatment such as: urinary continence, preservation of upper urinary tract and genital function and cosmesis.

Stjernqvist et al. showed a median of 12 procedures to achieve good results in bladder exstrophy staged approach (MSRE) (8). There are few experiences with one-stage reconstruction: Gargollo et al. had a mean of 4 (range 1 to 31) procedures to achieve satisfactory results (9). Ebert et al. reported mean of 2.95 (range 1 to 8) surgeries in patients who underwent single stage repair, with only 13.6% requiring more than 4 surgeries, about half of these patients were referred after failed reconstruction elsewhere (10). In our series, around 73.3% (11 out of 15) of patients were referred after failed reconstruction, and a mean of 3±1.1 procedures (range 2-5) per children was observed, and we still have six patients waiting for additional surgeries.

The incidence of urinary continence after bladder exstrophy repair is variable (12% to 83%) (11-15). Various factors interfere with results analysis. There is no standard definition for continence and as a result studies address continence in a non-uniform way. Patient age at bladder closure, the type of closure performed, the number and type of procedures required to establish continence, the need for concomitant bladder augmentation and the need for clean intermittent catheterization is not reported in most papers. Again, there are few cases treated with one-stage reconstruction. Mitchell and colleagues showed 74% (17 of 23 patients) of daytime continence. Overall, 2 of 10 boys (20%) with bladder exstrophy achieved primary daytime continence with one-stage reconstruction alone and without the need for further bladder neck reconstruction (16). In parallel, we showed 60% of our cohort (9 of 15 patients) continent, but only two (13.3%) achieved continence with one-stage reconstruction alone. This result indicates that one-stage reconstruction alone was mostly not able to give continence and bladder neck surgery is usually necessary.

The incidence of progressive or severe hydronephrosis and/or renal scarring ranges from 0% to 30% after one-stage reconstruction. Later surgical repair of vesicoureteral reflux was necessary in 0-50% of patients (17). In our series, three (20%) patients developed vesicoureteral reflux that required treatment.

The limitations of our study are that the experience with one-stage reconstruction was relatively small and not all patients underwent complete treatment to evaluate the efficacy of this procedure. However, we do believe it has advantages over the traditional approaches to bladder exstrophy. Based in our experience, one-staged reconstruction without osteotomy is feasible at any age, even after previous failed procedures, reducing the surgical steps and facilitating closure of the structures. It helps minimize the total number of surgeries. Improved urethral resistance may increase bladder capacity in young patients and restores bladder cycling, which results in the expansion of even very small reconstructed bladders with poor bladder plates (18, 19). While increased outlet resistance may allow for an increase in bladder capacity, a recognized consequence is elevated bladder pressure, which may lead to upper tract changes. It enables concomitant abdominoplasty, with good cosmetic results. Primary or secondary bladder neck reconstruction is required for optimal continence. In our pool of patients treated with primary repair, the need for bladder augmentation is still significant, but complications are less frequent than in the staged procedures.

Although there is ongoing discussion with regards to achieving continence in exstrophy patients, a successful primary bladder closure, regardless of the use of osteotomy or type of repair undertaken, has been shown to be the single most important predictor of eventual continence (20). Pelvic osteotomy remains to have a role in the surgical management of the exstrophy-epis-

padias complex, as it decreases tension across the abdominal wall, reduces the pubic diastasis, and helps restore the pelvic ring and floor to the normal anatomical configuration. However, in our series, it was not necessary to perform pelvic ostheotomies and bone mobilization, as we opted to use groin flaps for the abdominoplasty. It is necessary to wait for rectus anterior sheets consistency, which occurs usually after 45-60 days of life. The main reason for us to adopt this approach was that most of our patients were referred after failed attempt and these older children are less amenable to collaborate with traction needed after ostheotomies.

Another advantage of our technique in comparison to Mitchell's one-stage reconstruction is that we do not perform complete penile disassembly, reducing risks of penile ischemia and loss (Figure-1). In our series, ischemic loss of the glans or corporal bodies was not observed.

CONCLUSIONS

Most patients with bladder exstrophy will require multiple operations to achieve normal voiding and provide cosmetically acceptable and functional genitalia. One-stage reconstruction minimizes the number of surgical procedures required to achieve the treatment goals (urinary continence, normal genital cosmesis and preservation of upper urinary tract). The advantages of using groin flaps over current techniques for complete repair are the small risk for penile tissue loss and the avoidance of pelvic ostheotomies. The major drawback of this technique is the necessity to correct the bladder exstrophy defect after 45-60 days of life (wait to rectus anterior sheets consistency) and also a theoretical risk of malperfusion and loss of flaps, which was not observed in this study.

CONFLICT OF INTEREST

None declared.

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CHALLENGING CLINICAL CASES

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Intraoperative breakage of Sachse's knife blade: a rare complication of optical internal urethrotomy (one case managing experience)

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ABSTRACT

Optical internal urethrotomy (OIU) is the most common procedure performed for short segment bulbar urethral stricture worldwide. This procedure most commonly performed using Sachse's cold knife. Various perioperative complications of internal urethrotomy have been described in literature including bleeding, urinary tract infection, extravasation of fluid, incontinence, impotence, and recurrence of stricture. Here we report a unique complication of breakage of Sachse knife blade intraoperatively and its endoscopic management.

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Urethra; Recurrence; Methods

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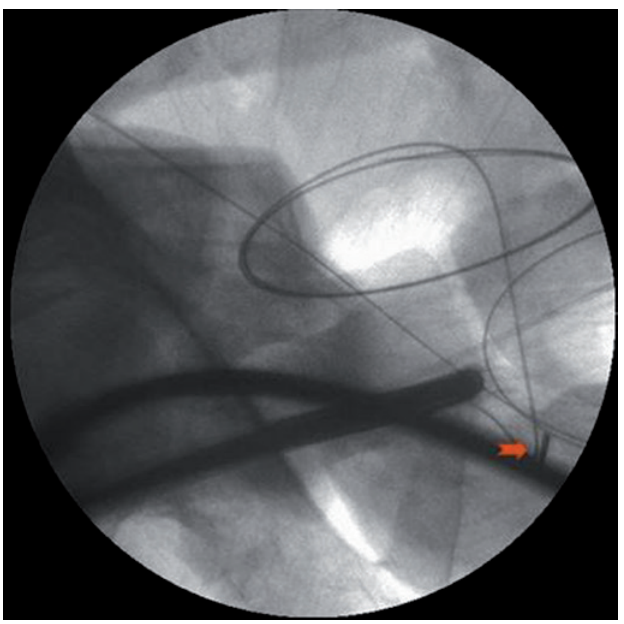
INTRODUCTION

Optical internal urethrotomy (OIU) is the most common procedure performed for short segment bulbar urethral stricture worldwide (1). However, its success rate is variable, and ranges from 35-60% (2, 3). This procedure is most commonly performed using Sachse's cold knife (4), although recently lasers have been introduced in the urological armamentarium for internal urethrotomy. Various perioperative complications of internal urethrotomy have been described in literature, including bleeding, urinary tract infection, extravasation of fluid, incontinence, impotence, and recurrence of stricture (5). Here we report a unique complication of breakage of Sachse knife blade intraoperatively and its endoscopic management.

Case Report

A 30 year-old male presented with complaint of lower urinary tract symptoms for the last six months. Uroflowmetry voiding pattern was suggestive of urethral stricture disease. Retrograde urethrography (RGU) revealed a short segment bulbar urethral stricture (<1.5cms). Optical internal urethrotomy was performed. Intraoperatively blade of Sachse's urethrotome accidently broken and fell proximal to the stricture which was

Figure 1 - Fluroscopic view of broken blade in bulbar urethra.



confirmed on fluoroscopy (Figure-1). We completed the procedure with another working element. During the procedure broken blade migrated to bladder (Figure-2). We retrieved the blade into the cystoscope sheath (22Fr) with the help of double J stent removing forceps. Cystoscope, sheath, forceps and the broken blade were withdrawn from the urethra as a single unit (Figure-3).

Figure 2 - Cystoscopic view of holding broken blade with Double J removal forceps.

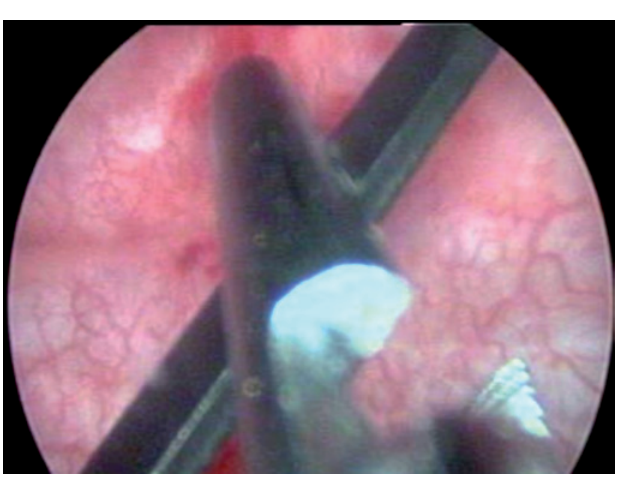


Figure 3 - Removal of knife blade.

DISCUSSION

Optical internal urethrotomy became popularized after the work of Sachse in 1971 (6) and now it is the preferred treatment modality for a short segment urethral stricture. This is the most favored procedure among the urologist as it is less morbid and minimally invasive day care surgery which is appealing to both patient and surgeon. The most common complications are recurrence of the stricture and bleeding (7, 8). The purpose of this case report is to highlight the unique complication of intraoperative breakage of knife blade and its endoscopic management. One should not start this (neither any other) procedure not being prepared to all its complications and that blade breakage is one of these, making necessary a blade backup and a double-J forceps available before starting this procedure. To the best of our knowledge, this is the only case report which describe this unique complication and management.

CONCLUSIONS

This complication should be kept in mind and instruments should be checked properly by the operative surgeon prior to start the procedure. Retained sharp objects like knife blade in urethra as a result of breakage of Sachse knife blade can be managed endoscopically.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Urologic surgery laparoscopic access: vascular complications

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ABSTRACT

Vascular injury in accidental punctures may occur in large abdominal vessels, it is known that 76% of injuries occur during the development of pneumoperitoneum. The aim of this video is to demonstrate two cases of vascular injury occurring during access in laparoscopic urologic surgery.
The first case presents a 60-year old female patient with a 3cm tumor in the superior pole of the right kidney who underwent a laparoscopic partial nephrectomy. After the Verres needle insertion, output of blood was verified. During the evaluation of the cavity, a significant hematoma in the inferior vena cava was noticed. After the dissection, a lesion in the inferior vena cava was identified and controlled with a prolene suture, the estimated bloos loss was 300ml.
The second case presents a 42-year old female live donor patient who had her right kidney selected to laparoscopic live donor nephrectomy. After the insertion of the first trocar, during the introduction of the 10mm scope, an active bleeding from the mesentery was noticed. The right colon was dissected and an inferior vena cava perforation was identified; a prolene suture was used to control the bleeding, the estimated blood loss was 200mL, in both cases the patients had no previous abdominal surgery.
Urologists must be aware of this uncommon, serious, and potentially lethal complication. Once recognized and in the hands of experienced surgeons, some lesions may be repaired laparoscopically. Whenever in doubt, the best alternative is the immediate conversion to open surgery to minimize morbidity and mortality.

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EDITORIAL COMMENT: UROLOGIC SURGERY LAPAROSCOPIC ACCESS: VASCULAR COMPLICATIONS

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Branco et al. (1) describe two cases of injuries during laparoscopic renal surgery; both recognized immediately and repaired laparoscopically. Laparoscopic entry complications are an uncommon but potentially life-threatening complication of laparoscopic surgery. Most such injuries occur during initial trocar insertion and most commonly involve major vessels and/or bowel. Failing to recognize these immediately is a leading cause of death in patients (2). A review by the U.S. Food and Drug Administration (FDA) committee found that there was insufficient evidence to recommend any particular access technique over the others (veress needle, direct trocar and hasson) largely due to poor centralized reporting of these complications (3). Whilst laparoscopic renal surgery is safe even in patients with previous abdominal surgery (4), surgeons must be experienced with access techniques, select patient appropriately for laparoscopic procedures, be familiar with trocar designs, use safe trocar insertion techniques and be vigilant for injuries during access. Whilst some of these injures may be amenable to laparoscopic repair, one should have a low threshold for conversion to open and seeking appropriate help (general or vascular surgeon) when necessary to manage these promptly and safely.

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EDITORIAL COMMENT: UROLOGIC SURGERY LAPAROSCOPIC ACCESS: VASCULAR COMPLICATIONS

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In the video by Branco et al. (1) two vascular injuries are shown. The video is very illustrative on how injuries are recognized and more important the way they are repaired. A quick intraoperative diagnosis of the injury and an appropiate management was performed by the surgeons.

Altough uncommon, an important percentage of injuries in laparoscopic procedures occur during the abdominal access using needles or trocars. In a recent Cochrane Systematic Review, no difference was found between direct trocar over Veress needle entry in terms of injuries (2). Complications can be minimized, but they can never be avoided. We have to know how to solve them when present. And as the authors mention in the abstract, you should never hesitate on converting to open surgery when necessary.

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VIDEO SECTION

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Laparoscopic cystoprostatectomy for bladder cancer in a male patient combined with open ileal conduit urinary diversion

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BACKGROUND AND OBJECTIVES

Although open radical cystectomy remains the gold standard treatment for muscle invasive bladder cancer (MIBC), laparoscopic cystoprostatectomy (LCP) has proven to be safe, and along with the robot-assisted technique is gaining more space. In this video, we describe the steps of LCP, featuring our approach. With the combination of extirpative stage surgery with conventional reconstructive part (Bricker ileal conduit), our goal is to offer the advantages of a minimally invasive approach with oncological and perioperative safety.

MATERIALS AND METHODS

Patient, 57 years ago, T2aN0M0, with erectile dysfunction and ECOG-0. Neoadjuvant chemotherapy with gemcitabine and cisplatin was used (4 cycles). The bowel was prepared by oral self-administration of 1 liter of electrolyte solution. Prophylaxis with a cephalosporin was administrated for 5 days and Enoxaparin 40mg was administered preoperatively and until postoperative day 8. We used the five-port transperitoneal approach. The surgery was performed in May/2014 at the Institute of Integrative Medicine Prof. Fernando Figueira - IMIP, Recife-PE/Brazil.

RESULTS

The operative time was 160 minutes. The oral diet was resumed on the 3rd postoperative day (POD). Estimated blood loss of 700ml. Postoperatively, recovery was uneventful and the patient was discharged on the 4th POD. During the 10 month-follow-up, no major complications occurred. Only a left hydronephrosis (G1) was found in abdominal US performed in the 3rd month of follow--up, but didn't show complications so far. There wasn't tumor recurrence and no adjuvant therapy was required.

CONCLUSIONS

LCP is a feasible and safe procedure, with a promising future in minimally invasive surgical procedures technique.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robot – assisted laparoscopic retroperitoneal lymph node dissection in testicular tumor

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ABSTRACT

Introduction and objective: Retroperitoneal lymph node dissection (RPLND) is indicated for patients with non-seminomatous germ cell tumor (NSGCT) with residual disease after chemotherapy. Although the gold standard approach is still the open surgery, few cases of robot-assisted laparoscopic RPLND have been described. Herein, we aim to present the surgical technique for robot-assisted laparoscopic RPLND.

Patient and method: A 30 year-old asymptomatic man presented with left testicular swelling for 2 months. Physical examination revealed an enlarged and hard left testis. Alpha-fetoprotein (>1000ng/mL) and beta-HCG (>24.000U/L) were increased. Beta-HCG increased to >112.000U/L in less than one month. The patient underwent a left orchiectomy. Pathological examination showed a mixed NSGCT (50% embryonal carcinoma; 30% teratoma; 10% yolk sac; 10% choriocarcinoma). Computed tomography scan revealed a large tumor mass close to the left renal hilum (10x4x4cm) and others enlarged paracaval and paraortic lymph nodes (T2N3M1S3-stage III). Patient was submitted to 4 cycles of BEP with satisfactory response. Residual mass was suggestive of teratoma. Based on these findings, he was submitted to a robot-assisted RPLND.

Results: RPLND was uneventfully performed. Operative time was 3.5 hours. Blood loss was minimal, and there were no intra- or postoperative complications. The patient was discharged from hospital in the 1st postoperative day. Pathological examination showed a pure teratoma. After 6 months of follow-up, patient is asymptomatic with an alpha-fetoprotein of 2.9ng/mL and an undetectable beta-HCG.

Conclusion: Robot-assisted laparoscopic RPLND is a feasible procedure with acceptable morbidity even for post chemotherapy patients when performed by an experienced surgeon.

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VIDEO SECTION

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Megalourethra and urethrorectal fistula: a rare presentation and a challenging reconstruction

Antonio Macedo Jr. [1], Sérgio Leite Ottoni [1], João Luiz Gomes Parizi [1], Gustavo Marconi Caetano Martins [1], Gilmar Garrone [1], Marcela Leal da Cruz [1]

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INTRODUCTION

Congenital megalourethra is a rare genital anomaly characterized by dilatation of the penile urethra with or without evidence of proximal or distal urethral obstruction. The urethra shows lack of corpus spongiosum and in some cases corpora cavernosa in the region of the distal urethra. The absence of these structures causes a ballooning of the urethra despite no mechanical obstruction. Some authors have also reported cases with prune-belly syndrome–like features (1, 2), so as the presence of urethral duplication (3).

We want to present a patient treated in our institution with megalourethra and urethrorectal fistula.

MATERIAL AND METHODS

An 8-month male patient presented to our institution with history of anal micturition and an enhanced flaccid penis lacking corporal tissue. Physical examination showed a megalourethra and a rectal urethra at the anal border. The VCUG combined to retrograde urethrogram showed a normal bladder, a rectal urethra and a ballooned penile urethra, which ended blinded at the bulbar area without communication to the proximal segment. No previous history of UTIs and renal damage was found. We performed an ASTRA approach and isolated the rectal urethra, creating a perineal stump. We reconstructed the anal canal over the external sphincter. We then assessed the penile urethra by a longitudinal ventral incision enabling complete exposition of the dilated urethra. We dissected the distal penile urethra, which was opened and aligned to the perineal urethral stump by means of a termino-terminal anastomosis. We tailored the penile urethra over a 10F silicone tube and excised the redundant tissue. Finally, the penile skin was readapted after discarding the redundant skin. An indwelling tube was left for 10 days. Patient had a satisfactory outcome and excellent cosmetic result.

DISCUSSION

Megalourethra is a rare malformation. Absence of the corpora cavernosa explains the massive dilatation of penile urethra despite mechanical obstruction. Congenital megalourethra has been classified into scaphoid and fusiform types and is usually associated with additional urinary tract and other system anomalies, irrespective of its type and severity. Amsalem et al. (4) reported on ten fetuses with megalourethra that were identified at a median gestational age of 19 (range, 13-24) weeks and all were confirmed postnatally or at autopsy. Three pregnancies were terminated and seven continued. All

cases presented with a distended bladder and megalourethra and all cases had normal karyotype. Of seven liveborn babies, one died in the neonatal period due to pulmonary hypoplasia. All six infants alive had a dysfunctional urethra and three suffered from impaired or end-stage renal disease. Associated anomalies were found in half of the cases.

Operative technique for megalourethra with genital malformation has to be tailored to each individual case, depending on the intraoperative and endoscopic findings.

CONCLUSION

Congenital megalourethra is caused by abnormal development or hypoplasia of the penile erectile tissue. When the amniotic fluid volume is normal, survival is possible but sexual dysfunction is expected. Urethroplasty follows the same principles of hypospadia repair.

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

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EDITORIAL COMMENT: MEGALOURETHRA AND URETHRORECTAL FISTULA: A RARE PRESENTATION AND A CHALLENGING RECONSTRUCTION

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Macedo et al. (1) present a video that elegantly demonstrates a one-stage repair for a child with a urethrorectal fistula along with a megalourethra. The anterior sagital trans-ano-rectal approach (ASTRA) was first described by Di Benedetto and Di Benedetto for use in clitoro-vaginoplasty (2). The ASTRA approach allows careful separation of the urethra and the rectum. It has proven to be useful in the treatment of urethral trauma, urogenital sinus anomalies, and urethral duplications (3). This video, when combined with the authors' previous work, provides a useful reference to anyone planning to use this technique (4).

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