Photomicrographs comparing normal and diabetic groups. The arrows point to the epithelial flaking resulting in the agglomeration of the cells in the tubular lumen in the diabetic groups. (page 819)

A - Control Group; B - ALA Group; C - Diabetic Control Group; D - Diabetic ALA Group. (HE, 200x)
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Boa leitura.
Age and Body Mass Index: the most important factors of urinary and erectile function recovery after robotic assisted radical prostatectomy

The July–August 2019 issue of the International Brazilian Journal of Urology presents original contributions with a lot of interesting papers in different fields: Infertility, Bladder augmentation, Bladder Cancer, PCNL, Prostate Cancer, Renal Cell Carcinoma, Partial nephrectomy, Renal stones, Nocturnal Enuresis, Basic Research, Laparoscopic Surgery, Penile Cancer, Stress Urinary Incontinence and Adrenalectomy. The papers come from many different countries such as Italy, Brazil, USA, UK, Turkey, China, France, Iran, Republic of Korea, Argentina, India and Spain, and as usual the editor’s comment highlights some papers. We decided to comment the paper about a very interesting topic: Robotic-Assisted Radical Prostatectomy (RARP).

Doctor Neumaier and colleagues from the FMUSP, Brazil performed on page 703 (1) an interesting study about the factors involved in urinary continence and sexual potency recovery after robotic-assisted radical prostatectomy (RARP). They studied 104 patients operated by two surgeons between 2008 and 2015, with a minimum 12 months follow-up. The patient features (age, body mass index, PSA, date of surgery and sexual function), tumor features (tumor stage, Gleason and surgical margins) and follow-up data (time to reach urinary continence and sexual potency) were collected at 1, 3, 6 and 12 month and every 6 months thereafter. Until the end of the study, only one patient was incontinent and 20.7% were impotent. The authors concluded that the age was a predictor of urinary and erectile function recovery in 12 months and the body mass index was significant factor for potency recovery.

With the introduction of robotic surgery, some technical difficulties in laparoscopic surgery were lessened, due to, among other factors, the three-dimensional field of vision, hand tremor filtration and greater ergonomic freedom of movement of the surgeon (2-7). RARP in comparison with the open radical prostatectomy is associated with smaller positive surgical margins for pT2 tumors and better sexual function results during 12 months, and less impairment of urinary function during 12 months (8).

Retrospective studies indicate that urinary control rates are better in younger patients, although there is conflicting data in the literature (9-12). This can be explained by the degeneration of the rhabdosphincter, which occurs with age. In this paper the authors had 16 patients with body mass index (BMI) ≥ 30 kg/m2 at the time of surgery and there was no statistical difference in recovery of urinary continence compared to patients with BMI < 30 kg/m2, but the average time to reach urinary continence was almost double for obese patients. The present paper also confirms that the age in an important factor to impotence recovery. We congratulate the authors for this very important contribution.
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Bladder cancer (BCa) is the second most common genitourinary malignancy with 81,190 estimated new diagnoses for 2018 in the United States alone (1). Radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) and perioperative chemotherapy is the standard treatment for recurrent high risk non-muscle invasive and for muscle invasive BCa (2). However, RC as well as perioperative chemotherapy represent a complex procedure associated with high perioperative morbidity and mortality as a consequence also of the characteristics of the population which is generally affected by multiple comorbidities when compared to other surgical procedures (3, 4). One of the strategies proposed to reduce the perioperative morbidity and mortality consists in the application of an Enhanced recovery after surgery (ERAS) program (5). It consists in a multidisciplinary, multi-element care pathway that aim to standardize and improve perioperative management. ERAS program was firstly introduced in colorectal surgery, where ERAS or fast track surgery pathways have been developed to accelerate recovery by attenuating the stress response. Thereafter, a metanalyses have provided level 1 evidence reporting a reduction of complications, and hospital stay for colorectal surgery patients where ERAS was applied (6, 7).

ERAS protocol has been also proposed in the field of RC, however at the time only limited evidences exist (8, 9). It is an approach comprehensive of preoperative, perioperative and postoperative interventions. During the consensus (5) 34 points were individuated. A preoperative counselling and education with verbal and written information regarding surgery, urinary diversion and planned early recovery is necessary to involve the patient in the therapeutic management. In this period several assessments have to be proposed: a preoperative medical optimization, nutritional assessment, visit by a stoma nurse with advice on stoma and neobladder care, cardiopulmonary exercise testing if indicated, advice and support for cessation of smoking and social issue addressed and discharge planning. Smoke cessation in this setting has been demonstrated to be highly effective in increasing survival and perioperative outcomes after RC (10). These elements required a multidisciplinary team composed by urologists, nurses, nutritionists and social workers.

The day before RC, a carbohydrate loading is required, while no bowel preparation is recommended. The day of RC, solids up to 6 hours and clear fluids up to 2 hours preoperative including carbohydrate loading are permitted. From the
anesthetic point of view, no long acting sedatives and a thrombosis prophylaxis with compression stocking and low molecular weight heparin is recommended. Only a limited antimicrobial prophylaxis and skin preparation with clorexdine-alcool. A minimally invasive approach with robotic assisted radical cystectomy is recommended. Fluid restriction and prevention of hypothermia with removal of nasogastric tube in recovery. In the day 2-4 after cystectomy, prevention of postoperative nausea and vomiting, use of chewing gum and unrestricted diet. Drain fluid routinely sent for creatinine at day 2 and drain removed if drain fluid indicates serum creatinine levels. Thrombosis prophylaxis with compression stockings and low molecular weight heparin. Early mobilization, daily nutritional supplements with nutrition goal of 900 kcal/d, fluid/electrolyte, encourage self-care. At day 4, discharge at home is possible when criteria met: pain adequately controlled, independently mobile, regular diet/normal bowel function, component with neobladder or stoma care. These elements seem particularly difficult to be applied in real life setting where the type of health care system are very different across the countries. In fact, a discharge at day 4 seem feasible only in the presence of sub-acute facilities care or dedicated nurse that might help the patients to return to the normal life. At 10 postoperative day is programmed a postoperative visit with the removal of stent 10 without a stentogram and the removal of clips.

The proposal of an optimal international accepted pre, intra and postoperative management of RC patients is an important guide for all the urologists around the world. However, some criticism must be highlighted. First, the number of elements that has to be considered for defining an ERAS protocol is arbitrary. The definition of ERAS itself might be tricky with several articles in the literature which proposed different ERAS approaches comprehensive by different elements and therefore it has really to be questioned if it possible to test an approach comprehensive by so different numbers of elements. A consensus has been developed by world recognized urologists but it remains an expert opinion and therefore a low level of evidence (5), therefore there might be other elements non-included in it or centers claiming to do ERAS but not respecting all the points suggested. In this context it is difficult to understand the differential impact of every point in reducing perioperative morbidity and mortality. Second, not all the elements included in the RC ERAS have the same level of evidences. For example, in contemporary patients, the use of the robotic approach has rapidly increased, surpassing in selected American and European centers the traditional open approach (11). However, the use of robot instead the classic open surgery seem not have (12) enough evidences to be included in the ERAS protocol and its presence in the ERAS protocol seem not justified.

In this sense, ERAS protocol seems an important way to standardize the management of RC candidates. However, there is a need to evaluate in detail every single element included in this protocol before accepting it in the normal routine. The more elements from the ERAS proposal one takes, the better the outcome should be. In the future a standardized ERAS basic approach should be clearly defined and then the intervention is to be particularized by each institution and each patient. ERAS should be evaluated and eventually adopted by each Institution on the basis of their own resources, needs and cultural differences.

REFERENCES


A comprehensive literature-based equation to compare cost-effectiveness of a flexible ureteroscopy program with single-use versus reusable devices

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ABSTRACT

Purpose: to critically review all literature concerning the cost-effectiveness of flexible ureteroscopy comparing single-use with reusable scopes.

Materials and Methods: A systematic online literature review was performed in PubMed, Embase and Google Scholar databases. All factors potentially affecting surgical costs or clinical outcomes were considered. Prospective assessments, case control and case series studies were included.

Results: 741 studies were found. Of those, 18 were duplicated and 77 were not related to urology procedures. Of the remaining 646 studies, 59 were considered of relevance and selected for further analysis. Stone free and complication rates were similar between single-use and reusable scopes. Operative time was in average 20% shorter with digital scopes, single-use or not. Reusable digital scopes seem to last longer than optic ones, though scope longevity is very variable worldwide. New scopes usually last four times more than refurbished ones and single-use ureterorenoscopes have good resilience throughout long cases. Longer scope longevity is achieved with Cidex and if a dedicated nurse takes care of the sterilization process. The main surgical factors that negatively impact device longevity are lower pole pathologies, large stone burden and non-use of a ureteral access sheath. We have built a comprehensive financial cost-effective decision model to flexible ureteroscope acquisition.

Conclusions: The cost-effectiveness of a flexible ureteroscopy program is dependent of several aspects. We have developed a equation to allow a literature-based and adaptable decision model to every interested stakeholder. Disposable devices are already a reality and will progressively become the standard as manufacturing price falls.

INTRODUCTION

Flexible ureterorenoscopes are expensive to acquire and have limited longevity (1). The significant improvements in flexible ureterorenoscopes have made flexible ureteroscopy the main treatment modality to target upper urinary pathologies, especially stone disease (2-4). The low invasiveness of the procedure has made it popular worldwide. Nevertheless, there is growing concern globally regarding its high costs (5). Also, one must consider the costs of the laser machine
used for stone fragmentation, personnel to take care of cleaning and sterilization processes, and all the disposable instruments used within the flexible ureteroscope procedure which have made it so efficient. Finally, when a reusable scope breaks, some institutions may experience a significant delay for its replacement or repair, obligating to have more than one device so that the surgical program is not suddenly interrupted (3-5).

On the other hand, we are now entering in the era of single-use devices (6). In principle, the disposable ureterorenoscopy eliminates the high costs of reusable scopes purchase and repair. It also abolishes the theoretical risk of cross infections and the need for a sterilization process. Additionally, some advocate that the disposable scope allows more torque in the instrument during a stone treatment procedure without the fear of breakage, pushing flexible ureteroscopy boundaries further.

The purpose of this study was to critically evaluate all studies concerning the cost-effectiveness of flexible ureteroscopy comparing single-use with reusable scopes in order to create a comprehensive equation to allow a literature-based decision.

MATERIALS AND METHODS

A systematic online literature review was performed in PubMed, Embase and Google Scholar databases. The following key words were used to attain relevant studies regarding flexible ureteroscopy using reusable and disposable scopes: “flexible” combined with the terms “ureteroscopy”, “ureteroscope”, “ureterorenoscopy”, “ureteroscopic”, “ureteropyeloscopy”, “durability”, “longevity”, “cost-analysis”, “digital”, “fiber-optic”, “single-use”, “disposable”, “reusable”, “renal”, “urinary” and “sterilization”.

We performed the review of all published studies on flexible ureteroscopy in order to establish a literature-based decision model for flexible ureteroscope acquisition. For that, we aimed to answer pre-defined questions formulated by two experienced endourologists (GSM and FCT) who work on private and public institutions with different medical reimbursement policies and distinguished surgical supplies used for endourological procedures. These queries were designed to evaluate the clinical and economic impact of the type of flexible ureteroscope used on daily practice and are the following:

1) Are the stone free and complication rates different between single-use and reusable flexible ureteroscopes?
2) Is the operative time different between single-use and reusable flexible ureteroscopes?
3) Does surgeon experience impact clinical and economic outcomes in an individualized manner between single-use and reusable scopes?
4) Is the longevity of digital and optical flexible ureteroscopes different? Also, is it different between new and refurbished scopes?
5) Does the sterilization method influence permanent scope longevity?
6) What is the impact of stone burden and surgical instrumentation on ureteroscope longevity?
7) How may we generate a cost-analysis equation based on the above-mentioned criteria to allow an objective and literature-based decision model to elect the most suitable flexible ureteroscope acquisition policy for our institution?

Our procedure for evaluating records identified during the literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria (7). All the relevant studies were gathered, organized, and brought to discussion. Two separate urologists performed the online search and reviewed all papers considered suitable and relevant for this analysis. Because of the paucity of high-quality publications, not only prospective assessments but also case control and case series studies were included in the final analysis.

RESULTS

After extensive review of the literature, 741 studies with the previously elected terms were found (Figure-1). Of those, 18 were duplicated and 77 were not related to urology procedures and were excluded. Of the remaining 646 studies, 59 published between 2000 and 2018 were considered of relevance. The studies details are exposed
on Table-1. The experts who carefully selected all studies formulated literature-based answers to the articulated questions and developed a comprehensive decision-model equation for maintaining a flexible ureteroscopy program.

**Stone Free and Complication Rates**

Somani et al. published a study comparing reusable digital versus fiber optic flexible ureteroscopes and the results were similar in terms of accessibility to the entire collecting system and stone-free rates (SFRs). Complication rates were similar between the two modalities (5). Nevertheless, the authors did not use disposable scopes.

The Polyscope™ has been introduced in urologic armamentarium as a modular, semi disposable flexible ureterorenoscope system (8). One

<table>
<thead>
<tr>
<th>Study Design</th>
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<tr>
<td>Randomized controlled trials</td>
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<tr>
<td>Animal feasibility study</td>
<td>19</td>
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<td>Bench top studies (Level evidence 4)</td>
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**Flexible Ureteroscope Included**

- Olympus URF-P3 14,26,30,39,43,48,55,62,66
- Olympus URF-P5 5,9,18,19,33,44,46,54,61
- Olympus URF-P6 10,13,49
- Karl Storz Flex-X 14,30-32,39-41,50,59
- Karl Storz Flex-Xc 11,28,35,45,47,57,58,60,61
- ACMI DUR-8 / DUR-8 elite 14,29,30,33,36,37,39,59
- Richard Wolf 7330/1 14,26,30,39,63,64
- Richard Wolf Cobra 20,24
- Richard Wolf Viper 33
- ACMI AUR-7 26
- Stryker Flex Vision U-500 33
- Olympus URF-V 5,18,27,28,51,52
- ACMI/Olympus DUR-D 38
- Karl Storz Flex-Xc 11,20,24,25,28,35,42
- LithoVue™ 10,11,13,20,22-24,42,51,52
- Polyscope™ 8,9,15,16,21,34
- SemiFlex™ 14
- Pusen™ 23
- YouCare Tech YC-FR-A™ 24
- Neoscope NeoFlex™ 24
study prospectively compared clinical outcomes of the Polyscope™ with reusable Olympus fiberoptic URF-P5 scope (9). After including 180 patients in each arm, the single session SFR postoperatively for Polyscope™ and URF-P5 was 76.7% versus 69.4% (p=0.12), respectively. However, for lower calyceal stones, URF-P5 was significantly better than Polyscope™ (82.0% vs. 69.2%; p=0.022), respectively. The complication rate was 15.3% versus 15% (p=0.3), respectively. Urosepsis occurred in 5% of patients in the Polyscope™ group and 3.3% in the reusable scope cohort (p=0.42).

Usawachintachit et al. performed a more recent prospective case-control study in which LithoVue™ was compared to Olympus fiberoptic URF-P6 (10). A total of 116 cases were performed with single-use scope and 65 cases with reusable scopes. The number of patients with no fragments, insignificant residual fragments (≤2mm) and significant fragments (>2mm) was 60.0%, 12.5%, 27.5% for LithoVue™, and 44.7%, 13.2%, 42.1% for URF-P6 (p=0.36), with a tendency towards better outcomes with the single-use scope. Mager et al. (11) prospectively compared 68 consecutive procedures using reusable flexible ureterorenoscopes (Flex-X2 S/Flex-X C , Karl Storz) with 68 consecutive procedures utilizing single-use digital flexible ureterorenoscopes (LithoVue™). Patients had same stone burden and demographic characteristics. The authors found non-significant different SFR (82% vs. 85%; p=0.8) and complication rates (7 vs. 17%; p=0.06) with reusable and single use scopes, respectively. One febrile urinary tract infection (UTI) occurred in the single-use group and none in the reusable scope cohort.

Regarding perioperative complications, UTI remains a feared hurdle following ureteroscopy. A study in France reports that acute pyelonephritis is a rare complication of ureteroscopy (2.4%) (12). In the study by Usawachintachit et al. (10), the complication rate was lower in the LithoVue™ group compared to the URF-P6 group (5.4% vs. 18.0%; p <0.05). Interestingly, there were three cases of UTI in each arm. Similar rates of UTIs were seen in other studies comparing single-use with reusable scopes (9, 11).

As the last generation single-use devices have shown similar characteristics to reusable ureterorenoscopes, allowing similar SFRs, the price analysis may be performed with the knowledge that differences in cost do not translate in surgical outcomes inconsistency. In the same sense, a cost reduction, no matter towards single-use or reusable scopes, will not impact morbidity.

Operative Time

One study prospectively comparing the Polyscope™ single-use flexible ureteroscope with reusable scopes found similar mean procedure duration: 73±27 versus 74±13min (p=0.99), respectively (9). In this study, both types of flexible ureteroscopes, disposable and reusable, were fiberoptic.

In the study by Somani and coworkers (5), the authors found that the digital flexible scope allowed a decreased operative time by 20% with similar SFR. In the study by Usawachintachit et al. (10), the overall mean procedure duration was 10.4 minutes shorter for LithoVue™ than with fiberoptic URF-P6 (64.5 vs. 54.1min;p <0.05). This difference broadened to 13 minutes and remained statistically significant in cases performed for stone removal (70.3 vs. 57.3min;p <0.05). This was translated in shortened operating room duration in stone removal cases with LithoVue™ (104.3 vs. 89.8min, respectively; p <0.05).

In a subsequent study from the same group, Tagushi et al. (13) prospectively compared flexible ureteroscopy with the fiberoptic Olympus URF-P6 and LithoVue™ in a micro-cost analysis. They found a non-significant 19.8 min (93.4 vs. 73.6min; p=0.09) or 21% shorter total operative time with the digital single-use scope. This was translated in a mean reduction from US$ 1.618.72 to US$ 1.348.64 per procedure. In the study by Mager et al. (11), the author compared reusable scopes (Flex-X2 S/Flex-X C , Karl Storz) with single-use LithoVue™ and found similar operative time (76.2 vs. 76.8min; p=0.9). However the authors did not compare the specific operative time of single-use versus digital (Flex-X C ) and fiberoptic (Flex-X2 S ) reusable scopes.

By analyzing the above-mentioned data, the final equation for calculating cost of a flexible ureteroscopy program should include an ope-
rative time factor and a higher effectiveness is achieved with digital scopes.

**Surgical Expertise Impact on Ureteroscope Efficiency**

Several studies have evaluated the mechanical, optical and irrigation properties of single-use ureterorenoscopes (8, 9, 14-24). The more recent single-use scopes have good performance and do not lack in endurance and maneuverability compared to permanent equipment. A recent multi-institutional, prospective, comparative study by Usawachintachit et al. paralleled procedural outcomes between LithoVue™ and reusable ureteroscopes (10). The authors found that the LithoVue™ was associated with a shorter learning curve and had comparable procedural outcomes and complication rates when matched with reusable flexible optical ureteroscopes. Nevertheless, no dedicated learning-curve investigation was performed. The fact that a digital scope was compared to a fiberoptic one might explain the results.

There are no studies comparing scope longevity regarding single surgeon versus multiple surgeon’s use. However, a recent case series of flexible ureteroscopy using the Storz digital Flex-X³ by a single expert urologist with more than 1000 flexible ureteroscopies performed has shown long scope longevity with a single scope lasting 159 cases (25). It is common sense that inexperienced surgeons have a higher chance of damaging the flexible ureterorenoscope if not properly supervised. As all surgical procedures, there is a learning curve that must be respected. Unfortunately, no study was able to identify the learning curve effect on single-use versus reusable scopes and this could not be included in the final equation for calculating the cost of a flexible ureteroscopy program.

**Longevity of digital, optical, new and refurbished flexible ureteroscopes**

In average, a digital ureteroscope is used 21 times before requiring repair, while the average fiberoptic ureteroscope is only used 6-15 times before going back to the manufacturer (26, 27). In a recent study by Legemate et al. (28), reusable digital scopes had a slightly longer longevity (mean 27 cases; 20-56) compared to fiber optic flexible ureteroscopes (mean 24 cases; 10-37). However, a wider look at all published literature reveal that new flexible scopes may last 5 to 159 cases (25-52). In comparison, the average longevity of refurbished flexible scopes ranges from 3 to 11 cases (35-39). In addition, one study suggests that not only brand-new flexible ureteroscopes are more resistant to damage (mean of 44 usages in this specific trial) than devices refurbished, but that scopes last more if they are repaired by original manufacturer (mean 11.1) than by outsourced vendors (mean 6.9 cases) (36).

In modern series with single-use flexible scopes, the resilience of the equipment was proved to be adequate even for long cases (9, 10, 13, 16). In the European prospective multicentric clinical study by Doizi et al. (17), however, there were two failures with LithoVue™ (5%), which demanded the surgeons to use the permanent scope to finish the case. Scope longevity impacts the number of repair orders and was included in the final equation.

**Sterilization method impact on scope longevity**

Different series investigating flexible ureteroscope breakage report that it may occur outside of the operating room, during processing and storage in 7.7 to 22% of times, even in the hands of experienced and dedicated staff (26, 29). Abraham et al. (40) studied two identical fiber optic ureteroscopes that underwent two different sterilization processes: Steris 1 (peroxyacetic acid 35%; 30min cycle at 50°-56°C) and Cidex OPA (Johnson and Johnson Co., Irvine, CA; glutaraldehyde 2.4%; 30-40 min. soak cycle at room temperature followed by a rinse in sterile water). The authors have demonstrated that after 100 cycles, the first ureteroscope, which was sterilized in the Steris system, had a 12mm tear on its shaft, 297 damaged fibers, and a 37% drop in resolution. Conversely, the second ureteroscope, which was sterilized with Cidex, had no visible external damage and had only 10 damaged fibers.

In a clinical trial by McDougall et al. (48), a new Olympus URF-P3 flexible ureteroscope was used for two 30-day independent study periods during which a single surgeon used the endoscope for a variety of upper urinary tract procedures. During the first 30-day period (11 cases; operative
time of 457 min.), the endoscope was cleaned by the endourology support team using the Steris 20. During the second 30-day period (15 cases; 618 min.), a separate endoscope was cleaned only by the surgeon using the Cidex technique. In follow-up evaluation of the flexible ureteroscopes, there was no change in the angle of flexion or deflection in either group during the study period and leak-proof-pressure testing was acceptable in both endoscopes. In Steris group, no optical fibers were noted to break during use. In Cidex group, during the study, eight fibers were broken. These findings are in discordance with the study by Abraham et al. (40). Still, the authors believe this was specifically related to a higher prevalence of lower pole stone location in the Cidex cohort and not to the sterilization process itself.

When we look at scope longevity, series that report longer scope duration are in general those where they were sterilized on Cidex and not Steris. Carey et al. report new scope duration of at least 48 cases using Cidex method (29). Delfidio et al. report fiberoptic ureteroscope duration of more than 100 cases for two scopes with the same process (32). Multescu et al. achieved the noteworthy mark of 159 procedures with a single digital Storz Flex-X2 (25). On the other hand, in a recent series by Mager et al. where Steris was the sterilization method (11), in 68 procedures utilizing reusable flexible ureterorenoscopes (Flex-X2 and Flex-X2S), 9 repair orders were needed caused by 5 damages of brand new and 4 damages of used instruments. In the study by Semins et al. (45), after all urology nurses had been educated by the charge nurse of the urology service as to the proper endoscope cleaning, processing, and sterilizing protocols with Steris system, the average number of uses per ureteroscope before repair was increased from 10.8 to 28.1, with a repair cost saving of US$ 300.00 per use.

Single-use scopes have the clear advantage of not requiring any sterilization process as they are discarded at the end of the procedure. Only a minimal recycling cost might be considered. This translates in having a new scope for every procedure, theoretical lower risk of cross infection, and less cost related to reprocessing, logistics and personnel required for the whole cycle of scope sterilization. The final formula for calculating costs of the flexible ureteroscopy program contains a specific factor of reprocessing or recycling cost per case.

Impact of stone burden and instrumentation on ureteroscope longevity

Several surgical and patient factors might affect stone free rates, morbidity and ureteroscope longevity (45). Access sheaths have been shown to protect the kidney and the ureter during flexible ureteroscopy and to potentially increase SFR (53). A large retrospective cohort confirmed the safety of the ureteral access sheath but failed to show any improvement in the stone free status among patients with compared to those in which the access sheath was not used (54). Pietrow et al. have reported that the routine use of ureteral access sheaths, miniaturized nitinol baskets and smaller laser fibers will minimize the strain placed on a ureteroscope during a procedure, ultimately increasing the flexible ureteroscope longevity (55). Other investigators have also suggested that the routine use of a ureteral access sheath may also help to improve the durability of the flexible ureteroscope since it provides continuous ureteral access, reduced ureteral trauma, and shorter operative times (56). Multescu et al. advocate routine use of an ureteral access sheath and have recently published a case series using three new generation digital flexible ureteroscopes in which they lasted for 96, 151 and 159 cases (25). However, to date, there are no well-designed prospective randomized trials to provide strong evidence that the durability of the deflection unit of the flexible ureteroscope is preserved using this technique.

Jacquemet et al. (57) retrospectively compared the outcomes of flexible ureteroscopy for stone treatment in patients with calculi in the lower pole (n=232) versus with calculi in other kidney locations (n=139). Stone burden was similar between groups but stone size <10mm (61.2% vs. 48.5%; p=0.018) and use of an access sheath were more frequent in the lower pole cohort (80.2% vs. 66.9%; p=0.007). In only 19.8% of these cases the calculus was relocated to a more favorable position in the kidney. SFR was similar between groups (68.3% in lower pole group vs. 69.8%; p=0.77) with no difference in regards to
complication rates (9.1% vs. 7.9%, respectively; p=0.67). Jessen et al. retrospectively evaluated the influence of the collecting system anatomy on the efficacy and morbidity of flexible ureteroscopy and found that stone size, long infundibulum, and infundibulopelvic angle <30° negatively affected the SFR (58). Perlmutter et al. retrospectively evaluated the impact of stone location on 86 cases managed by flexible ureteroscopy and laser lithotripsy and also found that stone location did not significantly affect the SFR (59). Martin et al. retrospectively compared 89 cases of flexible ureteroscopy for lower pole stones with 73 cases with stones in other locations and on multivariate analysis the presence of multiple stones was the only statistically significant predictive factor of SFR (60). Similar findings were reported by Resorlu et al., who pointed as independent factors for success the stone size, number, composition, infundibulopelvic angle and renal malformations (61). The common intraoperative practice of stone displacement with a basket or grasper into the renal pelvis or upper pole for lithotripsy could explain these findings (62, 63).

Although most studies support that SFR are similar for lower pole and non-lower pole stone, there is increasing evidence that there is a correlation between the technical difficulty of the procedure and a higher incidence of ureteroscope malfunction (64, 65). Auge et al reported that in situ fragmentation of lower pole calculi is not possible in 28–34% of cases because of reduced ureteroscope deflection caused by the optical fiber (66). In those cases, potential harm to the scope occurs. In forced deflections where the laser fiber is unable to maintain total internal reflection, the photons may refract into the cladding and jacket rather than reflect back into the core fiber, with resultant fiber failure and ureteroscope damage (30, 31). Forbes et al. retrospectively analyzed laser fiber logs during flexible ureteroscopy for stone treatment and found that malfunction occurred in 8 of 142 cases [5.6%] (50). Importantly, all 8 cases were in procedures for lower pole stones (8 of 79; 10.1%) and resulted in flexible ureteroscope damage. The combination of aggressive active deflection of the flexible ureteroscope and simultaneous passage of the holmium laser probe may stress the fiberoptic system and result in fiber breakage. In a recent series by Ozimek et al., the authors evaluated their reusable flexible ureterorenoscopy program and found that in 32 of 423 (7.5%) cases the scopes were defective after the procedures (51). Thirty-one of 32 cases (96.86%) with proven scope damage were related to exploration of the lower pole and in 20 of 23 (86.96%) it was for stone treatment in that location. Hennessy et al. treated 234 patients for renal stone procedures with seven new Olympus URF-V instruments and had 15 major scope damages in a 30-month period (52). Staghorn stones (p=0.016) and stones in the lower pole calyx or mid zone calyx (p=0.074) were risk factors for scope damage.

Stone burden and instrumentation affect scope longevity and were considered in the final equation for computing flexible ureteroscopy program costs.

Cost-analysis decision model: creating a literature-based equation

The overall cost of a reusable scope must consider the financial expenditure for three main parameters: scope purchase, repair and sterilization. A recent series reported the cost of a new conventional flexible ureteroscope (Flex-X, Karl Storz, Germany) to be US$ 13,611 (41). The digital Olympus URF-V has been recently purchased by US$ 20,200 in an Australian series (52). The repair cost, diluted by case and scope longevity, also has a wide range in the literature from US$ 48 to US$ 605 per case (40-47, 51, 52). Both purchase and repair costs may be influenced by the business contract between the owner of the scope and the manufacturer or its dealer. The reprocessing or sterilization cost includes personnel (nurses, technicians), material for brushing, leakage testing, cleaning, packaging, and sterilization. If we do not consider the value of acquisition of STERRAD machine (system that use low-temperature, hydrogen peroxide gas plasma technology), recent cost-analysis studies show a reprocessing cost varying from US$ 19.9 to US$ 108.00 per case (11, 41, 49, 52).

When a disposable scope is being considered, repair should not be considered in the equa-
tion. Furthermore, there is no reprocessing, and this should be exchanged for recycling and labor. Tagushi et al. have shown a US$ 3.65 recycling cost per scope used (13). The main factor being considered for the single-use scope is always the purchase cost. This is mainly influenced by the generation of the disposable scope and by the business contract with the manufacturer. Recent purchase prices reported for the existing scopes are US$ 1300 to US$ 3180 for LithoVue™ (22, 42, 52, 53), US$ 700 for Polyscope™ (34), and US$ 800 for SemiFlex™ (14). As the manufacturing process of single-use scopes become more effective, less instruments are discarded and final retail cost may fall. Furthermore, selling price also decreases as more brands are competing for the market share.

A recent investigation by Martin et al. (42) assessed the economic consequences of reusable flexible ureteroscopes by performing a cost-benefit analysis on all flexible ureteroscopies. Permanent digital Flex-XC™ ureteroscopes were used in a total of 160 cases performed over a one-year period in which eight reusable scopes required repair. By using market price of LithoVue™, the authors linearly extrapolated the single cost to the amount of cases in order to estimate the total expenditure of their flexible ureteroscopy program if a single-use device was used. They have demonstrated a cost of US$ 848.10 per case and favored reusable ureteroscopes only after 99 procedures were performed. The authors finally suggested that high-volume institutions might find reusable ureteroscopes more cost beneficial. Mager et al. (11) also made a cost-analysis study and found that cost of reusable flexible ureterorenoscopy ranged between US$ 436 and US$ 708 per case. When taking into consideration the initial purchasing costs, it increased to US$ 1212-US$ 1743 per case. In their series, LithoVue™ had a price range of US$ 1300 (market price) to US$ 3180 (manufacturer’s suggested retail price) per procedure. In a prediction model, after 61 to 118 cases the routine use of a disposable scope would become more expensive than the routine use of reusable scopes.

In the German case series by Ozimek et al., the authors performed a retrospective evaluation of 102 diagnostic flexible ureteroscopies and 321 procedures for kidney stone treatment (51). The average number of cases resulting in scope damage was estimated to be 14.4 and the total cost of all procedures was estimated to be US$ 261.332. This resulted in an average cost per flexible ureteroscopy procedure of US$ 617.4 and the authors concluded that the reusable scope program was more cost-effective than if single-use scopes were employed since the assumed price per LithoVue™ device was US$ 1.227.5.

Hennessey et al. found a total repair cost for the 7 new digital scopes over the 30-month time period to be US$ 124.800, with a mean cost per case of US$ 533 (US$ 276-US$ 904) (52). The cumulative cost of 28 cases for the reusable flexible scope was approximately US$ 38.360. If the single-use scope (LithoVue™) was priced at US$ 1.918, then it would cost approximately US$ 55.239 for the same 28 cases and reusable scopes would be more economical. Conversely, if the single-use disposable scope was priced at US$ 920, then the cost for 28 cases would be around US$ 26.850 and this would represent a considerable economical saving. Figure-2 depicts the economic projection of published data mentioned above, which did not account for operative time costs.

After extensive review of literature, the authors of this study used all information gathered as answers to the pre-defined questions to build a comprehensive literature-based equation to allow a financial cost-effective decision model to flexible ureteroscope acquisition (Figure-3). The main drivers in the analysis are purchase and repair costs when a reusable scope is being considered. That changes to purchase and recycling cost if the potential buyer aims a single-use scope. In addition, if an Institution or Health Care System is acquiring the flexible ureteroscope, one should also consider in the equation the reprocessing cost for reusable scopes and operating room cost for any scope type. Reprocessing costs and operating room cost may be omitted in the equation if the potential buyer is the surgeon or an external company since their expenditures are not influenced by those factors. Finally, if the operating room time is being considered, digital scopes allow performing the same lithotripsy procedure with 20% less time. Therefore, the cost decreases and a 0.8 factor should be considered in this specific portion of the equation.
DISCUSSION

The first generation of disposable scopes had been tested and suboptimal surgical outcomes precluded their incorporation on daily practice (9, 15, 16). Newer scopes provide similar maneuverability and clinical efficacy to reusable scopes with equal low complication rates and are now part of the urology routine worldwide (10, 14, 17, 18, 20, 22-24, 42). Scope size seems not to be a significant issue for modern single-use digital scopes in comparison to reusable ureterorrenoscopes (10, 17, 18, 23). The trial by Usawachintachit et al. could even have shown superiority with LithoVue™ compared to a reusable scope if a larger sample size was included in the study (10).

Higher complication rates translate into prolonged hospitalization time, need for additional surgical procedures and medical treatment. In a recent study by Ofstead et al. where reprocessing practices of two institutions were evaluated, contamination was found in 100% of ureteroscopes after the sterilization process (67). The authors reinforce the need for frequent audits of reprocessing practices and highlight that the clinical implications of residual contamination and viable microbes found on sterilized ureteroscopes are still unknown. In that sense, no study has ever shown an inferior rate of urinary tract infection after flexible ureteroscopy with the employment of single-use devices (10). Therefore, the initial fear of cross infection with reusable scopes is not supported by existing literature and this is only a potential benefit from single-use scopes which has yet to be proven in clinical practice.

This study allowed us to perform an extensive review of published literature concerning flexible ureteroscope financial aspects. We have initially formulated questions to comprehensively evaluate all factors influencing flexible ureteroscope longevity and costs. The final formula was intended to contemplate the interests of specific parts involved in the flexible ureteroscopy industry: the surgeon who treats the patient, the manufacturer of the reusable or disposable scope, the producer of disposable instruments that sometimes is responsible for bringing the flexible scope to the operating field, and finally the institution where the ureteroscopy program takes place. So far, after extensive literature review, we may recommend using the last-generation, digital and high-performance single-use scopes in cases of high risk for ureteroscope damage. Also, when the market price of purchasing a new scope is elevated, or if ureteroscope repair price is high, migrating to single-use devices might be more cost-effective. In addition, academic centers may find a place for sin-
Single-use devices in hands-on courses and residency training. Finally, no instrument is failure-proof and a back-up device, single-use or not, should always be available in case a second scope is required to finish the case.

Our study has some minuses. First, it is a review of existing previous studies and only four prospective randomized trials were considered suitable for this analysis. There is a paucity of well-designed trials concerning flexible ureteroscopy and cost-effectiveness of the procedure, thought it has large application worldwide. A second point, we have not addressed the patient perspective since it does not influence the economic aspect of the process as long as acceptable surgical outcomes are respected. Nevertheless, we must not forget that in several health care policies, the patients are the ones who are paying for all the expenditures involved. Third, we did not evaluate disposable materials as they may vary according to surgeon preference, institution policy, and ultimately would not influence the flexible ureteroscope price. Fourth, for those who do not routinely use a ureteral sheath, the finding that the ureter or ureteropelvic junction might be too tight for scope passage can only be done with the disposable scope already opened, significant increasing the cost of the unsuccessful procedure if a single-use scope is being used. Another issue not included in the analysis is that for urologists performing flexible ureterorenoscopy in an outpatient setting with no direct access to a sterilization unit, higher sterilization costs and administrative work associated with external providers might favor single-use instrument instead of the reusable. Finally, we did not study the environmental impact of using disposable devices instead of reusable scopes. Yet, a recent analysis by Davis et al. has shown that the total carbon footprint of the lifecycle assessment of the LithoVue™ and reusable

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**Figure 3 - Literature-based equation to allow a cost-analysis decision model to flexible ureteroscope acquisition.**

<table>
<thead>
<tr>
<th>Total Cost Per Case</th>
<th>Sum of purchase costs / Number of cases</th>
<th>Repair cost per order X Number of repair orders</th>
<th>Reprocessing or recycling cost per case</th>
<th>[Sum of operating room hours X cost per hour] / Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider for single-use and reusable scopes</td>
<td>Consider only for reusable scopes</td>
<td>Consider in equation for single-use and reusable scopes</td>
<td>If scope buyer is a Health Care System, include this factor in equation; if buyer is the surgeon/external company, do not include.</td>
<td>If a digital scope is used (single-use or reusable), multiply total column cost by 0.8</td>
</tr>
<tr>
<td>To decrease purchase cost:</td>
<td>To decrease cost of repair order:</td>
<td>To increase scope longevity:</td>
<td>To increase scope longevity:</td>
<td></td>
</tr>
<tr>
<td>• Exclusivity contract;</td>
<td>• Exclusivity contract;</td>
<td>• Surgical training;</td>
<td>• Surgical training;</td>
<td></td>
</tr>
<tr>
<td>• Replacement contract;</td>
<td>• Replacement contract;</td>
<td>• Sterilization: dedicated staff solution method if allowed</td>
<td>• Sterilization: dedicated staff solution method if allowed</td>
<td></td>
</tr>
<tr>
<td>• Insurance.</td>
<td>• Insurance.</td>
<td>Routine use of ureteral access sheath</td>
<td>Routine use of ureteral access sheath</td>
<td></td>
</tr>
<tr>
<td>To increase scope longevity:</td>
<td>To increase scope longevity:</td>
<td>Lower pole stone repositioning</td>
<td>Lower pole stone repositioning</td>
<td></td>
</tr>
<tr>
<td>• Surgical training;</td>
<td>• Surgical training;</td>
<td>Avoid large complex stones or program staged procedures</td>
<td>Avoid large complex stones or program staged procedure</td>
<td></td>
</tr>
</tbody>
</table>

* It is advised to perform a historical analysis to decide if it is more cost-beneficial to buy a new scope or repair and on permanent one.

** The equation does not take into consideration the costs for STERRAD machine, video towers and disposable material other than the scope itself.

*** Having a backup flexible ureteroscope (single-use or not) is always advised in case of there is a main scope failure.
scope are not derisive and very similar, 4.43kg of CO2 and 4.47kg of CO2 per case, respectively (68).

CONCLUSIONS

The cost-effectiveness of a flexible ureteroscopy program is dependent of several aspects and not scope purchase price itself. Literature lacks well-designed prospective randomized trials investigating the economic aspects of flexible ureteroscopy with single-use and reusable ureteroscopes. Disposable devices are already a reality and will progressively become the standard as manufacturing price falls. We have developed an evidence-based equation that will allow future comparisons of flexible ureteroscopy program cost-effectiveness with reusable versus single-use scopes worldwide. The main factors involved are purchase price and repair requirement—both affected by exclusivity agreement, replacement contract and insurance; scope longevity—influenced by surgical training, sterilization method, stone burden and instrumentation; reprocessing or recycling expenditure; and finally operating room expense.

ABBREVIATIONS

SFR = stone-free rate
UTI = urinary tract infection
PRISMA = Preferred reporting items for systematic reviews and meta-analyses

CONFLICT OF INTEREST

None declared.

REFERENCES


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External validation of nomogram to predict inguinal lymph node metastasis in patients with penile cancer and clinically negative lymph nodes

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ABSTRACT

Introduction: Penile cancer (PC) occurs less frequently in Europe and in the United States than in South America and parts of Africa. Lymph node (LN) involvement is the most important prognostic factor, and inguinal LN (ILN) dissection can be curative; however, ILN dissection has high morbidity. A nomogram was previously developed based on clinicopathological features of PC to predict ILN metastases. Our objective was to conduct an external validation of the previously developed nomogram based on our population.

Materials and methods: We included men with cN0 ILNs who underwent ILN dissection for penile carcinoma between 2000 and 2014. We performed external validation of the nomogram considering three different external validation methods: k-fold, leave-one-out, and bootstrap. We also analyzed prognostic variables. Performance was quantified in terms of calibration and discrimination (receiver operator characteristic curve). A logistic regression model for positive ILNs was developed based on clinicopathological features of PC.

Results: We analyzed 65 men who underwent ILN dissection (cN0). The mean age was 56.8 years. Of 65 men, 24 (36.9%) presented with positive LNs. A median 21 ILNs were removed. Considering the three different methods used, we concluded that the previously developed nomogram was not suitable for our sample.

Conclusions: In our study, the previously developed nomogram that was applied to our population had low accuracy and low precision for correctly identifying patients with PC who have positive ILNs.

INTRODUCTION

Penile cancer is less frequent in Europe and in the United States than in other regions of the world. For instance, in South America and parts of Africa, the incidence of PC is high, where it can accounts for 1-2% of malignant diseases (1, 2) in men and represents an important public health issue.

Nodal involvement is the most important prognostic factor (3) in penile cancer, and curren-
tly available noninvasive staging methods have low sensitivity for detection of regional lymph node (LN) involvement. Optimal management of patients who are clinically node-negative (cN0) is still debated (4).

Inguinal LN dissection (ILND) can be curative; however, the procedure has high morbidity rates with respect to short- and long-term complications (5). On the other hand, surveillance strategies in patients with cN0 disease (intermediate/high risk, T1b or greater) have been associated with worse survival rates in recent non-randomized, retrospective studies (6-8).

Other alternatives, such as ultrasound-guided fine-needle biopsy, dynamic sentinel node biopsy (DSNB) (9, 10) or minimally invasive approaches, including pure laparoscopic or robotic-assisted ILND (11-14), have been described. However, these methods are dependent on technology, expertise, and have high costs; moreover, their advantages remain unclear.

Nomograms are low cost prediction tools for quantifying individual risk based on prognostic factors, which could be helpful in developing countries. For several cancers, nomograms might provide more precise prediction compared with the traditional tumor-node-metastasis (TNM) classification. Zhu et al. (15) developed a nomogram based on clinicopathological features (T stage, grade, lymphovascular invasion, p53 expression) of penile cancer and clinically negative inguinal LNs (ILNs). This nomogram was designed to predict ILN metastases in squamous cell carcinoma of the penis, to spare patients from unnecessary ILND, especially those living in poor countries. However, the nomogram still requires external validation. The objective of this study was to conduct external validation of the nomogram developed by Zhu et al. (15), based on our population.

**MATERIALS AND METHODS**

After receiving Institutional Review Board and ethics committee approval for the study, we included 65 men between 2000 to 2014 who underwent ILND as a part of treatment for primary penile squamous cell carcinoma and who presented with cN0 stage disease preoperatively. The definition of cN0 in our study was nonpalpable ILN. All patients were classified according to the European Association of Urology Risk Classification (EAURC) of penile cancer (16). In our routine practice, we normally suggest bilateral ILND for all patients who are classified as intermediate or high risk, according to the EAURC (17) ILND is generally performed 2–6 weeks after primary disease resection. The time from presentation to primary disease treatment was unavailable because this information was unreliable in the medical records. All pathological reviews were performed by an uropathologist using primary tumor slides. Tumor stage was assigned using the 2002 American Joint Committee on Cancer (TNM) system (18). T2 stage was divided into two subgroups, as in the nomogram by Zhu et al., (15) based on depth of invasion (T2a and T2b, corpus spongiosum and corpus cavernosa involvement, respectively). We used T1a and T1b jointly as category T1 and used Broders system to classify the histologic grade (18) in the same manner as in the nomogram. Lymphovascular invasion and p53 expression (cut-off expression of 20%) (19) were also evaluated in our study. We collected data from patients at three different institutions, then we performed external validation of the nomogram by Zhu et al. (15).

**Statistical analysis**

Data were analyzed using frequency and percentages for qualitative variables and medians and ranges for continuous variables. Comparisons between groups were performed using the chi-square or Fisher’s exact test for qualitative variables and the Mann-Whitney test for quantitative variables. Performance was further quantified in terms of calibration and discrimination. Discrimination was quantified with the area under the receiver operator characteristic (ROC) curve. Calibration was estimated by graphic representation of the associations between observed outcome frequencies and predicted probabilities (calibration curves) for the patient groups. A logistic regression model for positive LNs was developed based on predictor variables: T staging, tumor grade, vascular invasion, and p53 expression. Statistical analyses were performed using two-sided p<0.05.
as significant. Models, statistics, and figures were prepared using IBM SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) and R 3.2.21 (http://www.cran.r-project.org).

We considered three different external validation methods for the nomogram by Zhu et al. (15): k-fold, leave-one-out, and bootstrap. We sought to validate and verify whether this nomogram was useful for the prediction of positive ILN with good estimates in terms of confidence intervals.

RESULTS

This study analyzed 65 men with stage cN0 (intermediate/high risk) penile cancer who underwent ILND for nonpalpable ILN (Table-1) from 3 institutions in Brazil. The mean age was 56.8±14.7 years (range, 25-86 years). Twenty-four (36.9%) patients presented with positive LNs (Table-1) on ILND. Either standard or modified ILND was performed in all patients. Superficial and deep ILN were removed. A median of 21 (range, 3-60) ILN was removed and the mean number of positive ILN was 2.4 (range, 1-12). T1 stage was observed in 16 (24.6%) patients, T2a in 25 (38.5%), T2b in 7 (10.8%), T3 in 16 (24.6%), and T4 in 1 (1.5%) patient. Low-grade tumor (G1) was observed in 20 (30.8%) patients and G2 (61.5%) in 40 patients (Table-1). Comparing stage and ILN metastases, 8/16 (50%) patients with T1 stage, 13/32 (40.6%) with T2 stage, 3/16 (18.8%) with T3 stage, and 0/1 (0%) with T4 stage had ILN metastasis, respectively.

Table 1 - Clinicopathological characteristics in 65 patientes with penile cancer.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± dp (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T stage</strong></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>16 (24.6)</td>
</tr>
<tr>
<td>T2a</td>
<td>25 (38.5)</td>
</tr>
<tr>
<td>T2b</td>
<td>7 (10.8)</td>
</tr>
<tr>
<td>T3</td>
<td>16 (24.6)</td>
</tr>
<tr>
<td>T4</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>G1</td>
<td>20 (30.8)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>40 (61.5)</td>
</tr>
<tr>
<td>G3</td>
<td>5 (7.7)</td>
</tr>
<tr>
<td><strong>Lymphovascular invasion</strong></td>
<td></td>
</tr>
<tr>
<td>Absente</td>
<td>56 (86.2)</td>
</tr>
<tr>
<td>Present</td>
<td>9 (13.8)</td>
</tr>
<tr>
<td><strong>p53 Expression</strong></td>
<td></td>
</tr>
<tr>
<td>Weak</td>
<td>32 (49.2)</td>
</tr>
<tr>
<td>strong</td>
<td>33 (50.8)</td>
</tr>
<tr>
<td><strong>p53 Expression</strong></td>
<td></td>
</tr>
<tr>
<td><strong>EAU risk classification</strong></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>14 (21.5)</td>
</tr>
<tr>
<td>High</td>
<td>51 (78.5)</td>
</tr>
<tr>
<td><strong>pN stage</strong></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>41 (63.1)</td>
</tr>
<tr>
<td>N1</td>
<td>11 (16.9)</td>
</tr>
<tr>
<td>N2</td>
<td>11 (16.9)</td>
</tr>
<tr>
<td>N3</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td><strong>Pathologic lymph node status</strong></td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>24 (36.9)</td>
</tr>
<tr>
<td>negative</td>
<td>41 (63.1)</td>
</tr>
</tbody>
</table>
In our study, tumor grade was not associated with LN involvement \((p=0.538)\). Regarding histology, we found 30.8\%, 61.5\%, and 7.7\% of tumors to be G1, G2, and G3, respectively (Table-1). On the other hand, only 4.8\% of patients with negative LNs had G3 disease. Lymphovascular invasion was present in 20\% of patients with positive LNs and in 10\% of patients with negative LNs. In univariate analysis tumor grade and lymphovascular invasion were strongly correlated with LN status \((p<0.05)\). In the multivariate analysis, only T stage was statistically significant \((p=0.015\); Table-2\).

Our study included the k-fold, leave-one-out, and bootstrap methods to evaluate the nomogram by Zhu et al. \((15)\). The bootstrap method determined that this nomogram is random and does not establish a pattern of prediction of metastasis. Validation using the k-fold method confirmed this, which we identified during the process of modeling. The predictors shown in the nomogram of Zhu et al. \((15)\) were not statistically significant predictors of ILN metastases in our study sample.

All three models showed a low \(R^2\) (Table-3). These findings demonstrate that the nomogram by Zhu et al. \((15)\) has a high probability of false negatives in our population. The distribution of the bootstrap test results is shown in Figure-1.

**DISCUSSION**

There are some nomograms in literature to predict inguinal lymph nodes, for example, one of them was reported by Ficarra et al. \((20)\) and included variables as tumor thickness, grown pattern, grade, LVI, local infiltration, cN stage. Other one was published recently by Peak \((21)\) that used only grade, cN stage, and LVI. Zhu’s nomogram used cT stage, grade, LVI and p53 expression and must be applied in N0 patients. We decided to validate Zhu’s nomogram because of that idea of use a biomarker as p53 expression in association with clinical data, however in our study, this nomogram applied in our population had low accuracy for identifying patients with penile cancer who had positive ILN. Our analysis showed an unde-

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% LNM</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>T stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>50.0</td>
<td>0.154</td>
</tr>
<tr>
<td>T2a</td>
<td>32.0</td>
<td>0.341 (0.111-1.049)</td>
</tr>
<tr>
<td>T2b</td>
<td>71.4</td>
<td>2.20 (0.399-12.120)</td>
</tr>
<tr>
<td>T3</td>
<td>17.6</td>
<td>0.075 (0.012-0.462)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>G 1</td>
<td>35.0</td>
<td>0.731 (0.282-1.893)</td>
</tr>
<tr>
<td>G 2</td>
<td>35.0</td>
<td>0.1489 (0.145-15.235)</td>
</tr>
<tr>
<td>G 3</td>
<td>60.0</td>
<td>1.489 (0.145-15.235)</td>
</tr>
<tr>
<td><strong>Lymphovascular invasion</strong></td>
<td>0.002</td>
<td>0.071</td>
</tr>
<tr>
<td>Absente</td>
<td>33.9</td>
<td>-</td>
</tr>
<tr>
<td>Present</td>
<td>55.6</td>
<td>5.965 (0.857-41.507)</td>
</tr>
<tr>
<td><strong>p53 Expression</strong></td>
<td>0.350</td>
<td>0.296</td>
</tr>
<tr>
<td>Weak</td>
<td>31.3</td>
<td>-</td>
</tr>
<tr>
<td>Strong</td>
<td>42.4</td>
<td>1.789 (0.602-5.318)</td>
</tr>
</tbody>
</table>
restimation of positive LNs. We would like to emphasize that in using the nomogram by Zhu et al. (15) here, we could not improve the selection of patients with positive or negative ILN.

The occurrence and extent of ILN metastasis are the most important prognostic factors in patients with penile cancer and usually imply worse oncologic prognosis (22). Up to 25% of patients with no palpable LNs have occult micrometastases that are not detected by physical examination (23-25), and imaging studies, such as computed tomography scan or conventional magnetic resonance imaging, are also unable to detect inguinal micrometastases (26). Consequently, it could be debated that lymphadenectomy should be performed for all patients with penile cancer (8, 27) because ILN status is the key prognostic factor for survival, and patients can be cured by undergoing ILND. However, this poses a dilemma because early ILND leads to high rates (up to 50%) (28) of complications with significant morbidity, such as infection and/or wound dehiscence, skin necrosis, lymphedema, lymphoceles, and other complications. Surveillance strategies can reduce cancer-specific survival (5, 7-9). Patient survival is over 90% with early lymphadenectomy and less than 40% in patients treated with a surveillance strategy and later lymphadenectomy for regional recurrence. The alternatives, including DSN (9, 10) or minimally invasive approaches such as pure laparoscopic or robotic-assisted ILND (11, 12, 29, 30), are dependent on technology and have high costs, which make them extremely difficult to use in underprivileged populations. Nomograms could be a very interesting tool for improving patient outcome, however in daily practice they are underutilized because the guidelines recommendation of ILND for intermediate- and high-risk tumors (16), other alternatives as DSN and also because of lack of external validation of the available monograms.

Our univariate analysis found that tumor grade and lymphovascular invasion had a strong correlation with LN status. In the multivariate analysis, only T stage was statistically significant. Lymphovascular invasion was the only statistically significant variable in the study published by Zhu et al. (15) whereas we did not find statistical significance for this variable in our study (p=0.212). In patients with positive LNs, 20.8% had lymphovascular invasion; this pathological finding was present in 9.7% of patients with negative LNs. The

| Table 3 - Comparison of results in 3 different external validation methods. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Calibration | Zhu’s Nomogram | K-fold | Leave-one-out | Bootstrap |
| R² | 0.445 | 0.228-0.424 | 0.254-0.389 | 0.012-0.520 |
| Brier | 0.116 | 0.170-0.195 | 0.169-0.186 | 0.141-0.230 |
| Discrimination | | | | |
| (ROC) Area under the curve | 0.851 | * | * | 0.783 |

* ROC curve was performed for bootstrap only.

Figure 1 - ROC curve generated by Bootstrap method.
lymphovascular invasion is a strong predictor of positive inguinal lymph nodes as showed in other studies by Ficarra et al. (31), and other nomogram developed using the National Cancer Database that included 1,636 men in their analysis (21). Our hypothesis is that we found significance only in univariate because of the limited sample.

Zhu et al. (15) developed their nomogram because of the unreliability of currently available modalities for detecting occult nodal involvement, the need for decisive management of regional LNs for improvement of long-term patient survival, and the challenge of avoiding overtreatment with potential treatment-related morbidity. We sought to validate this nomogram for the prediction and identification of patients at risk for nodal metastasis who could potentially be spared unnecessary ILND. In this nomogram, surveillance is recommended if the nomogram probability of positive nodes is 0.1 (10%). The nomogram represents an attempt to define an objective, systematic, standardized, multivariate model capable of providing individual pN stage predictions.

In our study, we performed ILND for cases with intermediate and high risk, according to EAU guidelines. Using this classification, we performed 41 unnecessary ILND and detected 24 cases of ILN metastasis. Considering the threshold of 10% prediction risk (Zhu et al.) in our study, we had 35 patients (62%) that underwent ILND unnecessarily (true negatives), and we would have missed 3 (12%) patients with LN metastasis (true positives). Using a threshold of 20%, 31 (59%) underwent ILND unnecessarily (true negatives) and we would have missed the same 3 (12%) patients with LN metastases (true positives).

Despite the fact that this nomogram is a noninvasive and low-cost approach, it requires external validation. The aim of the present study was to externally validate a predictive model for ILN metastasis in our cohort of patients who had undergone ILND. Only pN status performed adequately within our external cohort of patients, and this finding was consistent using different statistical means (i.e., overall performance, discrimination, calibration, and clinical usefulness).

The nomogram proposed by Zhu et al. (15) is basically a model that can be used to explain the variability of one or more variables and the association and correlation of this variability with other exploratory variables. The goal is to determine values for the parameters in the specified template that generate the best fit of the model to the data. The best model is the one that produces the least unexplained variability, subject to the restriction that all model parameters must be statistically significant. One of the most important principles concerning the process of modeling is simplification of the model. The principle of parsimony says that given a set of equally good possible explanations, the correct explanation is the simplest one. Accordingly, given a set of valid models, the best model is the one that: a) includes the least number of variables, B) is linear and contrasts with nonlinear models, C) is based on few statements, and D) recognizes that simple explanations are always preferable in comparison with complex explanations. In the case of the model proposed by Zhu et al. (15), only lymphovascular invasion was identified as a statistically significant predictor for positive ILN. We used the bootstrap method because this method is used to estimate the confidence interval of parameters. In the bootstrap method, we set the answer and performed resampling of predictors (1,000 times) to identify confidence intervals for the parameters of the logistic regression and to identify better and greater values for $R^2$, the c-index statistic, and Brier score. Using the k-fold validation method, we measured the accuracy of the model, i.e., the model’s ability to faithfully represent the sample data. We used a third-party validation method, the leave-one-out method, which is a generalization of the k-fold method, where the number of templates is equal to the size of the sample. The method is useful for evaluating the complete behavior of the model and for correcting defects of the model. Considering that, we identified the extremes of confidence intervals for the parameters of logistic regression. Again, we identified the values of $R^2$ statistics, the c-index, and Brier score. These analyses confirmed that in our sample, the model proposed by Zhu et al. (15) was inappropriate, and even cross-validation did not improve the model. In our sample, the predictors shown in the nomogram of Zhu et al. (15) were not statistically significant predictors of ILN. All models showed a low $R^2$, including with the bootstrap technique (between 0.228 and 0.424) and leave-one-out (between 0.254 and 0.389) method. In the bootstrap method, p53 expression was identified as a better parameter.
We found that accuracy of this nomogram was lower in our sample (area under the ROC curve, 0.79). The calibration plot showed underestimation of positive ILN. This indicates poor sensitivity, poor specificity, and a low positive likelihood ratio for the various values used in the nomogram by Zhu et al. (15). According to our findings, we would like to highlight that the nomogram by those authors does not have satisfactory performance in improving selection of patients with positive or negative ILN disease, even using a threshold of 10% or 20%. The applicability of models derived from cohorts in China may be questionable when transferred to Latin America. These results could be explained for some reasons: different population and race, low accuracy of Zhu’s nomogram, limited sample, lack of other biomarkers, etc.

The limitations of the present study are inherent to any retrospective series. The number of patients was small (N=65); however, considering the rarity of penile cancer, our sample size is similar to those in other published series in the literature. Our population was significant and sufficient for validation of the nomogram by Zhu et al. (N=110) in penile cancer. Lymphadenectomy templates were not standardized; however, the three institutions and the surgeons involved are experts in urologic oncology and have extensive experience in the management of penile cancer. Nevertheless, our data reflect a real-world, multicenter experience.

CONCLUSIONS

In our study, the nomogram by Zhu et al. (15) applied in our population had low accuracy and low precision for correctly identifying patients with penile cancer who have positive ILN. Our analysis showed an underestimation of positive LNs. Using this nomogram, we could not improve the selection of patients with positive versus negative ILN.

ABBREVIATIONS

PC = Penile cancer  
LN = Lymph node  
ILN = Inguinal LN (ILN)  
DSNB = dynamic sentinel node biopsy  
ILND = Inguinal LN dissection

EAURC = European Association of Urology Risk Classification

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CONFLICT OF INTEREST

None declared.

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Editorial Comment: External validation of nomogram to predict inguinal lymph node metastasis in patients with penile cancer and clinically negative lymph nodes

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In this interesting paper Dr. Maciel and colleagues from Sao Paulo – Brazil conduct an external validation of a previously developed nomogram (1) to predict inguinal lymph node (ILN) metastases in penile cancer in patients with clinically negative lymph nodes. The authors analyzed 65 men with penile cancer who underwent inguinal lymph node dissection. Of 65 men, only 24 (36.9%) presented with positive LNs. The authors concluded that the present nomogram applied in Brazilian population had low accuracy and low precision for correctly identifying patients with penile cancer who have positive ILN.

Penile cancer is a rare neoplasia with low incidence in developed countries. In Brazil the incidence rate of penile cancer is 2.9 – 6.8/100,000 inhabitants, resulting in this country having one of the world’s highest incidence rates for this neoplasm (2-4). The most common sites of penile cancer metastasis are the superficial and deeper nodes of the inguinal and iliac region. The occurrence and extent of inguinal lymphatic metastasis are the most important prognostic factors in patients with penile cancer and usually imply worse oncologic prognosis (5). Extended Inguinal lymphadenectomy (open, laparoscopic or robotic) is the most useful and commonly performed surgery for staging and to cure inguinal metastasis in penile cancer cases. Although it is a widespread technique, post operatory complications often occur (6-8).

This paper is very important, but in the future, papers with prospective studies and with a more significant sample will be necessary to confirm the application of this nomogram to predict inguinal lymphatic metastasis in patients with penile cancer.

REFERENCES


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Nonsecretory intestinocystoplasty: postoperative outcomes of 25 years


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ABSTRACT

Objective: The objective of bladder augmentation (BA) is to create a low-pressure reservoir with adequate capacity. Despite its benefits, the use of intestinal patches in bladder enlargement provides a high risk of developing complications and BA with demucosalised bowel represents a potential alternative. Therefore, this study evaluated urological parameters and long-term clinical follow-up of patients submitted to non-secretory BA in a single center with 25 years of experience.

Materials and Methods: Patients treated with BA underwent urological evaluation, which included history, physical examination and urodynamic study. The main urodynamic parameters (bladder capacity and bladder compliance) were assessed in the pre and postoperative moments, and compared by the Wilcoxon Signed Rank test. The main long-term complications were described.

Results: 269 patients (mean age 14±13 years, 47% male) underwent BA with the use of demucosalised intestinal segments. Among the patients in the sample, 187 (69.52%) had neurogenic bladder, 68 (25.28%) had bladder exstrophy, nine had tuberculosis (3.34%), four had a posterior urethral valve (1.49%) and one with hypospadia (0.37%). After the surgical procedure, a significant increment in both urodynamic parameters was found, with a 222% increase in bladder capacity and 604% in bladder compliance (p <0.001 in both analyzes). Mean follow-up time ranged from 2 to 358 months, with a median of 72 months (IQR 74-247). Among all patients, 5 presented spontaneous perforation.

Conclusion: The study showed statistically significant increase in both compliance and bladder capacity after non-secretory BA, with a low rate of severe complications.

INTRODUCTION

The use of intestinal segments in bladder augmentation has promoted important advances on finding new ways to deal with patients with noncompliant bladders. Nevertheless, there is a concern regarding specific characteristics of the intestinal epithelium that can result in complications in the medium and long-term follow-up, affecting quality of life and prognosis of the patients. Among the main drawbacks are calculus formation, mucus production, metabolic acidosis, urinary tract infections, intestinal obstruction and increased long-term risk of cancer (1, 2). On the
other hand, non-secretory bladder augmentation may represent a potential alternative. This study is an update of our experience with demucolised bowel segments for bladder augmentation (3-5).

**MATERIALS AND METHODS**

During a period of 25 years (January 1991-June 2016), all patients who underwent demucolised bladder enlargement in a single center were included in the study. This study was conducted after a detailed animal experiment (3, 4). Patients with age greater than 55 years and those who had malignant disease with a life expectancy of less than 10 years were excluded. The procedures for diagnosis and surgical technique have been described previously (3-6). All patients were submitted to urologic evaluation, which included medical history, physical exam and assessment of urodynamic parameters. Data on bladder capacity and compliance were used to evaluate results. The same equipment measured cystometric maximum bladder capacity and compliance. Expected bladder capacity according to the formula described by Houle et al. (7) was also used as a comparison. All procedures in the study were performed by or under the supervision of the first three authors, who have carried out the study from the experimental phase.

Among all surgical interventions, 222 (82.5%) were performed with sigmoid intestinal patches (Group-A) and 47 (17.5%) were performed using ileum intestinal patches (Group-B). Surgical intervention was performed as follows: In group A, the entire width of the bladder wall was opened, including the mucosa. In order to prevent retraction of the graft, a silicone bladder modeler was inserted inside the enlarged bladder. This model was filled with saline solution at volumes that ranged from 40 to 250mL and maintained for two weeks. During this same period, the ureters were catheterized. In group B, the process of de-epithelialization was facilitated by insertion of a Foley with a 30mL balloon inflated until 7-8mL. The amount of fluid within the balloon varied according to the characteristics of each patient’s pelvis.

Mean and standard deviation were used when there was normal distribution, and median and interquartile range (IQR) were used when distribution was non-normal. Normality of data was evaluated through histograms and the Shapiro-Wilk test. The Wilcoxon Sign-Rank test was used to compare if there was a statistically significant difference between preoperative and postoperative capacity and compliance. All statistical calculations were performed with SPSS software version 18.1®. In all situations, the maximum acceptable probability of error for rejection of the null hypothesis was 5% (p <0.05 and confidence interval of 95%). This study was approved by the Research Ethics Committee of the Center for Health Sciences, Federal University of Pernambuco (APPROVAL NUMBER: 2.430.399).

**RESULTS**

A total of 269 patients who had undergone bladder augmentation using de-epithelialized intestinal segments were prospectively studied between January 1991 and June 2016. Patient age varied from 3 months to 55 years, with mean age of 14±13 years, 47% male. Of these patients, 187 (69.5%) were diagnosed with neurogenic bladder, 68 (25.3%) had bladder exstrophy, 9 (3.3%) patients had been treated for urinary tuberculosis, 4 (1.5%) had sequelae of posterior urethral valves and 1 (0.4%) presented with female hypospadia (Figure-1). Ileum was chosen in cases of bladder exstrophy or when there was any problem with the
colon (previous surgeries). Follow-up time varied from 2 to 358 months, with median follow-up of 72 months (IQR 74–247).

Median preoperative and postoperative bladder compliance was 1.93mL/cm/H2O (IQR 1.91–1.95) and 13.6mL/cm/H2O (IQR 12.8–13.9), respectively (p <0.001) (Figure-2). This resulted in an increment of 604%. Median preoperative and postoperative capacity was 92.1mL (IQR 90–95) and 296.8mL (IQR 265–308), respectively (p <0.01), resulting in an increment of 222% (Figure-3). The mean expected capacity by Houle's formula was 269mL (6), lower than the postoperative capacity levels that were obtained in the sample.

A total of 27 patients presented some kind of complication (10%). Three patients (1.1%) developed peritonitis with complete dehiscence of the wound, 4 patients (1.4%) presented dehiscence of the colonic anastomosis and 5 patients (1.8%) presented spontaneous perforation. Throughout this period, 13 cases (4.8%) of bladder lithiasis were identified in patients with bladder exstrophy. In

**Figure 2 - Comparison of preoperative and postoperative bladder capacity.**

![Figure 2](image)

**Figure 3 - Comparison of preoperative and postoperative bladder compliance.**

![Figure 3](image)
this group, 6 patients had a periurethral constrictor implanted simultaneously, and 5 of these were removed due to urethral erosion. Four patients in the exstrophy-epispadia group underwent post-void catheterization due to significant post-void residue. Spontaneous perforations were observed in patients diagnosed with bladder exstrophy and neurogenic bladder. The five cases of spontaneous perforation occurred at the region where the anastomosis was made between bladder and demucolised tissue. Out of all spontaneous perforations, 2 happened with ileum patches and 3 with sigmoid patches. The first and second cases had diagnoses of bladder exstrophy and perforation occurred after 5 and 7 years; the other 3 cases were observed in with neurogenic bladder; the perforation occurred after 2 years, 3 years and 2 years and 7 months, respectively. All three patients underwent intermittent catheterization through the urethra. During the 25 years follow-up of this group of patients, 11 deaths were verified; however, none of them were related to the bladder surgical procedure. Of the total sample, 35 cases (13%) were considered failures.

DISCUSSION

The complications that are intrinsic to the traditional techniques of intestinal cystoplasty have made surgeons pursue alternative modalities of bladder augmentation over time. Non-secretory bladder enlargement has been presented as one of these alternatives, as it does not present the characteristic disadvantages of the secretory and absorptive function of the intestinal mucosa. To our knowledge there is no report in the literature of a prospective study of bladder augmentation for this period of time at the same institution and by the same team starting at experimental phase. Studies were published in periods of time around not below 5 years.

In the present study, we found a statistically significant increase in bladder compliance and capacity after non-secretory bladder augmentation. This result is in agreement with the current literature. In a recent study published by Odeh et al. (8), patients were compared regarding bladder augmentation techniques (traditional ileocystoplasty vs. ileocystoplasty with demucolised bowel) and followed for 14 years. Authors reported that there was an increase in bladder capacity in both groups (without significant intergroup difference), therefore supporting our results. Several other studies have demonstrated an increase in bladder capacity following non-secretory intestinal cystoplasty. Jung et al. (9) analyzed 34 patients who underwent demucolised intestinal cystoplasty with urothelial alignment. The authors described a 2.96-fold increase in bladder capacity, and a total of 13 patients (39.4% of the sample) were able to suspend the use of anticholinergic drugs after 47.3 months of surgery. In a study by Jednak et al. (10), the increase in bladder capacity was of 2.94 times.

Regarding the complications, we found an incidence of 1.8% of spontaneous perforations (5 cases), which is lower than the current literature statistics when compared with a similar method or with traditional ileocystoplasty. In a study by Shekarriz et al. (11), 133 patients underwent several types of bladder augmentation and were studied for a similar period. The authors found six cases of intestinal obstruction, 17 spontaneous perforations (13%), and 15 patients requiring surgical revision for other reasons (12). In a case-control study conducted by Odeh et al. (8), the authors reported an incidence of 10% of spontaneous perforations in the sample.

The incidence of bladder lithiasis was of 13 cases (4.8%), which represents a lower rate as compared to previous reports. Additionally, all cases happened in patients who had bladder exstrophy. In a retrospective study with 91 children that had undergone bladder reconstruction with various segments of the digestive tract over a period of 10 years, Hensle et al. (12) found an incidence of 44% of bladder lithiasis. Among patients with bladder exstrophy, 5 (25%) presented such situation. In a retrospective series performed by Blaivas et al. (13) with 71 patients submitted to enterocystoplasty, authors found 6% of recurrent bladder lithiasis. The bladder lithiasis cases accounted for 19% (13 of 68) of the sample of patients diagnosed with bladder exstrophy. It is worth mentioning that 6 patients who presented with bladder lithiasis in our cohort had a peri-urethral constrictor implanted simultaneously, 5 of which
were removed due to urethral erosion. Since no more artificial devices are currently used in patients with a diagnosis of exstrophy, we expect this incidence to reduce, since it is known that procedures on the bladder neck increase the incidence of lithiasis. On the other hand, long-term follow-up has shown a high incidence of device erosion both at subcutaneous port and cuff site. A new intraurethral removable device has shown considerable improvements in continence, quality of life and occurrence of symptomatic urinary tract infections (UTI). This device has been applied to females but possibilities to its use in males are open (14).

Despite the visible improvements, we must recognize that a failure rate of 13% is still not ideal. New developing technologies may help improve these results in the future.

CONCLUSION

During this 25 year follow-up study, non-secretory bladder augmentation promoted a significant increase in bladder compliance and capacity. As compared to traditional techniques of bladder augmentation, a lower number of complications was observed.

CONFLICT OF INTEREST

None declared.

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Decrease in skeletal muscle index one year after radical cystectomy as a prognostic indicator in patients with urothelial bladder cancer

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ABSTRACT

Purpose: The present study aimed to determine whether sarcopenia after radical cystectomy (RC) could predict overall survival (OS) in patients with urothelial bladder cancer (UBC).

Materials and Methods: The lumbar skeletal muscle index (SMI) of 80 patients was measured before and 1 year after RC. The prognostic significance of sarcopenia and SMI decrease after RC were evaluated using Kaplan–Meier analysis and a multivariable Cox regression model.

Results: Of 80 patients, 26 (32.5%) experienced sarcopenia before RC, whereas 40 (50.0%) experienced sarcopenia after RC. The median SMI change was -2.2 cm²/m². Patients with sarcopenia after RC had a higher pathological T stage and tumor grade than patients without sarcopenia. Furthermore, the overall mortality rate was significantly higher in patients with sarcopenia than in those without sarcopenia 1 year after RC. The median follow-up time was 46.2 months, during which 22 patients died. Kaplan-Meier estimates showed a significant difference in OS rates based on sarcopenia (P=0.012) and SMI decrease (P=0.025). Multivariable Cox regression analysis showed that SMI decrease (≥2.2 cm²/m²) was an independent predictor of OS (hazard ratio: 2.68, confidence interval: 1.007-7.719, P = 0.048).

Conclusions: The decrease in SMI after surgery might be a negative prognostic factor for OS in patients who underwent RC to treat UBC.

INTRODUCTION

Bladder cancer (BC) is one of the most common urinary tract malignancies worldwide (1-3). It is generally treated using transurethral resection of bladder tumor (TUR-BT) or radical cystectomy (RC), and systemic cisplatin-based chemotherapy is performed in cases of advanced or metastatic BC. However, because BC is a highly malignant tumor with a variable and unpredictable biologic potential, the survival forecast for patients remains poor (4, 5) The prognosis of BC is poor in elderly people and in those with serious comorbidities and poor performance status (6).

RC is the customary treatment for patients with muscle-invasive BC (MIBC), and it is also commonly used to treat selected patients with high-risk, non-muscle-invasive BC (NMIBC). A recent study reported that complications following RC are strongly associated with patient-
-related factors, such as age, performance status, and comorbidities (7). Moreover, numerous studies have demonstrated that frailty is associated with impaired mobility, disability, poor endurance, and prolonged hospitalization (8, 9). In particular, sarcopenia—skeletal muscle wasting—is a crucial physiological alteration underlying frailty that can emerge as a result of aging and malignant disease (10), and it has been identified as a prognostic factor for various cancers (11). In patients with BC who have undergone RC, sarcopenia is associated with poor survival (12). However, changes in the skeletal muscle index (SMI) after RC have not been established as a prognostic tool. The aim of the present study was to evaluate changes in the SMI 1 year after RC as a predictor of overall survival (OS) in patients with urothelial bladder cancer (UBC).

MATERIALS AND METHODS

Ethics statement

The ethics committee of Kyungpook National University Hospital reviewed and approved the current study protocol (approval number: KNUMC 2016-05-021). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This was a retrospective study performed after approval from the institutional review board, who stated that consent was not required.

Patients

The present study included 80 patients with non-metastatic UBC who had undergone RC (31 robot-assisted RCs and 49 open RCs) between August 2008 and May 2013 and who had serial axial computed tomography (CT) images showing sarcopenia both before and 1 year after the RC. Before RC, all patients underwent TUR-BT. Following histopathological examination and imaging studies, RC was performed. The indications for RC were as follows: MIBC without evidence of distant metastasis (clinical stage: T2–T4, Nx, M0), recurrent multifocal NMIBC refractory to repeated transurethral resection, and Bacille Calmette-Guerin (BCG)-resistant carcinoma in situ. The exclusion criteria were as follows: previous pelvic radiation, clinical stage M1, and prior combination surgery. Open RC was performed through a midline incision in the typical manner (13). Robot-assisted RC was performed using the same surgical procedure as reported by Bak et al. (1). Standard pelvic lymphadenectomy (both obturator and external iliac nodes) was performed in all patients, except for 1 patient undergoing robot-assisted RC and 6 undergoing open RC because of severe adhesions. The clinical T stage was based on the guidelines of the 2010 American Joint Committee on Cancer TNM staging system for BC (14). Histological grades were determined according to the 2004 World Health Organization (WHO) classification system (15). Patients with cT3, cT4, and node-positive disease (based on the analysis of CT images), but with good performance status, received at least 3 cycles of cisplatin-based neoadjuvant chemotherapy. Each patient was followed up and managed according to standard practice (16).

Image analysis

Patients underwent abdominal CT for initial cancer staging and routine diagnostic purposes. For each patient, a set of CT scans just before and a mean of 1 year after RC was selected. Quantitative assessment of muscle areas was performed using commercially available software (Terarecon 4.4.7, San Mateo, CA, USA) by a subspecialty-trained urogenital radiologist. The radiologist selected the single cross-sectional areas at the level of the third lumbar vertebrae (L3) in which both transverse processes could be fully seen. The cross-sectional areas (cm²) of all skeletal muscles at L3 were computed automatically by summing the appropriate pixels within the CT Hounsfield unit (HU) range of -29 HU to 150 HU (17). After applying a predefined HU threshold set for each slice, boundaries between the different tissues were corrected manually when necessary.

Definition of sarcopenia

Muscle area was normalized for the square of patient height in meters (m²) and reported as the lumbar SMI index (cm²/m²) (18, 19). In Figure-1 shows the CT scans and SMI values of an 82-year-old man before and at a mean of 1 year after RC. Sarcopenia was defined as a lumbar SMI of <43 cm²/m² for men with a body mass index
(BMI) of <25 kg/m², as a lumbar SMI of <53 cm²/m² for those with a BMI of ≥25 kg/m², and as an SMI of <41 cm²/m² for women, as recommended by Martin et al. (20).

Statistical analysis

Patients were divided into two groups of 40 based on their sarcopenic status one year after RC: non-sarcopenic patients and sarcopenic patients. Differences between the groups were evaluated using the chi-square test for categorical variables and Student’s t-test for continuous variables. Multivariable Cox proportional hazards models were used to test the associations between the variables and OS, with hazard ratios (HRs) and 95% confidence intervals (CIs) calculated for each factor. OS was measured from the date of diagnosis to death or final follow-up. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA), and P-values < 0.05 were considered statistically significant.

RESULTS

Of the 80 patients, 26 (32.5%) were sarcopenic before RC, whereas 40 (50.0%) were sarcopenic after RC. The median change in SMI was -2.2 cm²/m². In Table-1 presents patient demographics and preoperative characteristics according to SMI 1 year after RC. Age, sex, and BMI were not significantly associated with sarcopenia 1 year after RC (P>0.05). The mean preoperative SMI was 50.51 cm²/m² in non-sarcopenic patients, significantly higher than that in sarcopenic patients (43.76 cm²/m²; P<0.001). In the cohort of patients with sarcopenia after RC, 47.5% had been classified as sarcopenic preoperatively, while only 7 (17.5%) patients with preoperative sarcopenia were in the non-sarcopenic group after surgery (P=0.004). Higher clinical stage (≥T2) at latest TUR-BT was more prevalent in sarcopenic patients than in those without sarcopenia (65.0% vs 37.5%; P=0.014). Sarcopenia was not significantly associated with ASA classification, presence of carcinoma in situ, BCG instillation history, and neoadjuvant chemotherapy.

In Table-2 shows the relationship between sarcopenia after RC and clinicopathological features. Evaluation revealed that patients with sarcopenia had higher tumor stage and grade than those without sarcopenia 1 year after RC. The mean changes in SMI were -3.80 cm²/m² in sarcopenic patients and -1.12 cm²/m² in non-sarcopenic patients (P=0.001). Notably, patients with sarcopenia had significantly higher all-cause mortality rates than those without sarcopenia (P=0.012). Metas-
tasis rate did not differ significantly between the 2 groups \((P=0.104)\).

Twenty-two patients died during the median follow-up of 46.2 months. Kaplan-Meier estimates showed a significant difference in OS \((P=0.012)\) and SMI decrease \((P=0.025)\) between the 2 groups (Figure-2). In Table-3, we assessed the relationship between various measured parameters and OS. Although sarcopenia 1 year after RC was significantly associated with OS in univariable analysis, there was no statistical association between sarcopenia itself and OS in multivariable Cox analysis. As indicated by the multivariable analysis, the probability of OS increased greatly as SMI decreased. When other factors were adjusted for, pathological T stage

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<td>25 (62.5)</td>
<td>14 (35.0)</td>
<td></td>
</tr>
<tr>
<td>≥T2</td>
<td>15 (37.5)</td>
<td>26 (65.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Presence of CIS at latest TUR-BT</strong></td>
<td></td>
<td></td>
<td>0.712</td>
</tr>
<tr>
<td>No</td>
<td>35 (87.5)</td>
<td>37 (92.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (12.5)</td>
<td>3 (7.5)</td>
<td></td>
</tr>
<tr>
<td><strong>BCG instillation history</strong></td>
<td></td>
<td></td>
<td>0.712</td>
</tr>
<tr>
<td>No</td>
<td>37 (92.5)</td>
<td>35 (87.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (7.5)</td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Neoadjuvant chemotherapy</strong></td>
<td></td>
<td></td>
<td>0.762</td>
</tr>
<tr>
<td>No</td>
<td>34 (85.0)</td>
<td>33 (82.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (15.0)</td>
<td>7 (17.5)</td>
<td></td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists; BCG = Bacille Calmette-Guerin; BMI = body mass index; CIS = Carcinoma in situ; SMI = Skeletal muscle index; TUR-BT = Transurethral tumor resection of bladder tumor.
and an SMI decrease of ≥2.2 cm²/m² (HR: 2.689, 95% CI: 1.007-7.719, P=0.048) were found to be independent predictors of OS.

**DISCUSSION**

Muscle loss is expected in the elderly and is a rising concern in patients with cancer. Sarcopenia is characterized by decrease in protein synthesis and an increase in protein degradation (21). Hence, the condition displays many similar characteristics and can be a broad and integrated sign of cancer cachexia. Several recent studies have revealed definite connections between sarcopenia and mortality after RC to treat UBC (12, 22). To our knowledge, our current report was the first to indicate that changes in SMI after RC are associated with OS in patients with UBC. In particular, we observed greater all-cause mortality among patients who were sarcopenic after RC to treat UBC (40.0% vs. 15.0% in non-sarcopenic patients; P=0.012). The median OS was 43.5 months among patients with sarcopenia versus 48.1 months among those with normal SMI after RC. All-cause mortality was more prevalent in the sarcopenia group.

Table 2 - Comparison of clinicopathological variables according to skeletal muscle index one year after radical cystectomy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Non-sarcopenic patients, (n=40)</th>
<th>Sarcopenic patients, (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathological stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0, Tis, Ta</td>
<td>6 (15.0)</td>
<td>2 (5.0)</td>
<td>0.028</td>
</tr>
<tr>
<td>T1</td>
<td>15 (37.5)</td>
<td>10 (25.0)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>10 (25.0)</td>
<td>9 (22.5)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>4 (10.0)</td>
<td>13 (32.5)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>5 (12.5)</td>
<td>6 (15.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Histological grade</strong></td>
<td></td>
<td></td>
<td>0.029</td>
</tr>
<tr>
<td>Low</td>
<td>8 (20.0)</td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>32 (80.0)</td>
<td>39 (97.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph node involvement</strong></td>
<td></td>
<td></td>
<td>0.617</td>
</tr>
<tr>
<td>No</td>
<td>28 (70.0)</td>
<td>30 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (30.0)</td>
<td>10 (25.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphovascular invasion</strong></td>
<td></td>
<td></td>
<td>0.712</td>
</tr>
<tr>
<td>No</td>
<td>37 (92.5)</td>
<td>35 (87.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (7.5)</td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td><strong>SMI changes 1 year after RC (cm²/m²)</strong></td>
<td>-1.12±3.14</td>
<td>-3.80±3.59</td>
<td>0.001</td>
</tr>
<tr>
<td>Median follow-up period (months, range)</td>
<td>48.1 (14.4-105.1)</td>
<td>43.5 (12.5-93.0)</td>
<td>0.060</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td></td>
<td></td>
<td>0.104</td>
</tr>
<tr>
<td>No</td>
<td>29 (72.5)</td>
<td>22 (55.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (27.5)</td>
<td>18 (45.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall death</strong></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>No</td>
<td>34 (85.0)</td>
<td>24 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (15.0)</td>
<td>16 (40.0)</td>
<td></td>
</tr>
</tbody>
</table>
than in the cohort without sarcopenia, according to Kaplan-Meier analysis (log-rank test: \( P=0.012 \); Figure-2A). Likewise, Kaplan-Meier analysis also revealed that patients with larger SMI changes (\( \geq 2.2 \text{ cm}^2/\text{m}^2 \)) had a worse OS rate than those with smaller changes (\(<2.2 \text{ cm}^2/\text{m}^2\); log rank test; \( P=0.0025 \); Figure-2B). In our multivariate analysis, larger SMI decreases (\( \geq 2.2 \text{ cm}^2/\text{m}^2 \)) were associated with the risk of all-cause mortality (HR: 2.689, 95% CI: 1.007-7.719, \( P=0.048 \)).

Taken together with our results, sarcopenia and decreased SMI after RC are clinically useful and highly objective predictors of OS in patients with UBC who have undergone RC. Although sarcopenia one year after RC was significantly associated with OS in univariable analysis, there was no statistical association between sarcopenia itself and OS in multivariable Cox analysis. This suggested that the change in SMI was more useful for prediction of the OS after RC.

Table 3 - Multivariable Cox regression analysis of factors predicting overall death in patients with bladder cancer after radical cystectomy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.002</td>
<td>0.955 - 1.050</td>
<td>0.943</td>
<td>1.017</td>
<td>0.974 - 1.063</td>
<td>0.434</td>
</tr>
<tr>
<td>Gender</td>
<td>0.359</td>
<td>0.078 - 1.660</td>
<td>0.190</td>
<td>0.615</td>
<td>0.137 - 2.768</td>
<td>0.527</td>
</tr>
<tr>
<td>Pathological T stage</td>
<td>1.835</td>
<td>1.191 - 2.827</td>
<td>0.006</td>
<td>1.664</td>
<td>1.062 - 2.607</td>
<td>0.026</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>1.329</td>
<td>0.515 - 3.424</td>
<td>0.556</td>
<td>1.719</td>
<td>0.675 - 4.383</td>
<td>0.256</td>
</tr>
<tr>
<td>Grade</td>
<td>1.315</td>
<td>0.133 - 12.977</td>
<td>0.815</td>
<td>1.381</td>
<td>0.149 - 12.815</td>
<td>0.776</td>
</tr>
<tr>
<td>Sarcopenia 1 year after RC (No vs. Yes)</td>
<td>1.714</td>
<td>0.645 - 4.558</td>
<td>0.280</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMI decrease (&lt; 2.2 vs. ( \geq 2.2 \text{ cm}^2/\text{m}^2 ))</td>
<td>2.689</td>
<td>1.007 - 7.719</td>
<td>0.048</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cl = confidence interval; HR = hazard ratio; SMI = skeletal muscle index.
In this regard, previous studies have also reported that lower SMI and sarcopenia are modifiable prognostic factors in patients with UBC who have undergone RC. For instance, Psutka et al. showed that preoperative sarcopenia was independently associated with both increased cancer-related death and all-cause mortality in a multivariable analysis (22). In another study by Hirasawa et al. involving patients with UBC, preoperative sarcopenia was a significant independent predictor of unfavorable outcome, clinical T stage, hydronephrosis, histological type of TUR-BT specimens, and neutrophil-to-lymphocyte ratio (12). Conversely, a report by Smith et al. implied that sarcopenia was not significantly associated with worse OS rate (23). In the present study, preoperative sarcopenia was not associated with any clinicopathological features or prognoses. However, sarcopenia one year after RC was significantly associated with various pathological features, including tumor state ($P=0.028$), tumor grade ($P=0.029$), and OS. We also observed that SMI change was a useful predictor of OS after RC. Therefore, we suggest that postoperative CT should be performed and that clinicians should check the SMI during follow-up in patients with UBC. Nutritional support and the prevention of cachexia might be needed in selected patients with UBC who have undergone RC.

Sarcopenia may also predict complications and OS among patients with advanced or metastatic UBC who have undergone RC (21, 23, 24). In this regard, Wan et al. revealed that low SMI was frequently found in patients with BC who had undergone RC, and that this was strongly associated with early complications after surgery (24). Similarly, Smith et al. reported that sarcopenia was a predictor of major complications after RC in women, even after adjustment for known risk stratification characteristics (23). In advanced UBC, sarcopenia was useful in evaluating prognosis (21). More specifically, in a cohort of 88 patients with advanced UBC, the median OS rates were 11 and 31 months among sarcopenic and non-sarcopenic patients, respectively. In a multivariable analysis, sarcopenia was a significant and independent predictor of shorter OS (HR: 3.36). As sarcopenia reflects many clinical conditions, such as frailty, low nutritional status, active catabolism, and systemic inflammation, clinicians, including uro-oncologists, may use it for various purposes.

Several limitations of the current study must be acknowledged. First, the study had a retrospective design and involved a relatively small number of patients who underwent RC at a single institution. This may have led to sampling bias. Moreover, patients without available CT scans were excluded, which may also have caused selection bias. A prospective, randomized study involving a larger cohort and using multi-institutional methods will be required to confirm the present results. Second, the definition of sarcopenia was diverse in the present study. Although the volume of skeletal muscle mass differs according to ethnicity (25), the cut-off ranges defined in a previous Western study were within those determined in the present study. Considering ethnic and constitutional factors, a validated definition should be adopted in further studies. Despite these drawbacks, our present study presents a novel prognostic marker for predicting OS in patients with UBC who have undergone RC. The study indicated that the correction of sarcopenia after RC, as well as surveillance in selected patients, will improve postoperative management.

**CONCLUSIONS**

Sarcopenia and SMI changes one year after RC, which can be readily followed up using routine CT, might be effective predictors of OS in patients with UBC. This novel prognostic marker may assist in selecting patients with UBC who would benefit from nutritional support and interventions to prevent muscle wasting and consequent sarcopenia. The clinical utility of SMI changes as a prognostic marker merits further evaluation in prospective or external validation studies.

**ABBREVIATIONS**

BC = Bladder cancer  
RC = Radical cystectomy  
MIBC = muscle-invasive BC  
NMIBC = non-muscle-invasive BC
SMI = skeletal muscle index
OS = overall survival
UBC = urothelial bladder cancer
CT = computed tomography
TUR-BT = transurethral resection of bladder tumor
BCG = Bacille Calmette-Guerin
WHO = World Health Organization
HU = Hounsfield unit
BMI = body mass index
HR = hazard ratio
CI = confidence interval

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CONFLICT OF INTEREST

None declared.

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E-mail: uroyoo@knu.ac.kr
A comparison of perioperative outcome between robot-assisted and laparoscopic radical prostatectomy: experience of a single institution

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¹Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

ABSTRACT

Purpose: To compare perioperative and pathological results in different approaches of robotic or laparoscopic radical prostatectomy.

Materials and Methods: We retrospectively reviewed 206 patients diagnosed with prostate cancer (PC) from June 2016 to October 2017 in the First Affiliated Hospital of Nanjing Medical University. A total of 132 cases underwent robot-assisted laparoscopic radical prostatectomy (RLRP) including 54 patients on transperitoneal robot-assisted laparoscopic radical prostatectomy (Tp-RLRP) and 78 on extraperitoneal robot-assisted laparoscopic radical prostatectomy (Ep-RLRP). Meanwhile, 74 patients performed with extraperitoneal laparoscopic radical prostatectomy (Ep-LPR) were also included. Perioperative and pathological data were compared among these groups.

Results: All operations were completed without conversion. There was no significant difference in basic and pathological characteristics of patients between each two groups.

In Tp-RLRP vs. Ep-RLRP: Significant differences were found in the comparison in total operation time [235.98 ± 59.16 vs. 180.45 ± 50.27 min, P = 0.00], estimated blood loss (EBL) [399.07 ± 519.57 vs. 254.49 ± 308.05 mL, P = 0.0473], postoperative pelvic drainage time [5.37 ± 2.33 vs. 4.24 ± 3.08 d, P = 0.0237] and postoperative length of stay [8.15 ± 3.30 vs. 6.49 ± 3.49 d, P = 0.0068] while no significant differences were detected in other variables.

In Ep-RLRP vs. Ep-LPR: Longer total operation time was observed in Ep-RLRP when compared to Ep-LPR [180.45 ± 50.27 vs. 143.80 ± 33.13 min, P = 0.000]. No significant differences were observed in other variables.

Conclusion: In RLRP, Ep-RLRP was proved a safe and effective approach based on the perioperative results compared to Tp-RLRP. Ep-RLRP and Ep-LPR provides equivalent perioperative and pathological outcomes.

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INTRODUCTION

Prostate cancer (PC) is the second most common malignant tumor in men and an important cause of cancer-related morbidity and mortality worldwide. In 2017, the estimated new PC cases and deaths were 161,360 and 26,730 in the United States, respectively (1). Generally,
surgery is the standard of care for the treatment of localized disease to achieve an extended life expectancy.

Before minimally invasive surgery was widely used, open radical prostatectomy (ORP) had been a good alternative for the treatment of PC. However, high incidence of iatrogenic diseases caused by open surgery have led people to look for minimally invasive ways to improve perioperative and postoperative conditions.

Laparoscopic radical prostatectomy (LRP) technique was first systematically reported in 1997 by Schuessler (2) and relevant studies showed that this technique provides better perioperative and postoperative outcomes compared to ORP (3-5). In 2001, the first robot-assisted laparoscopic prostatectomy (RLRP) was reported by Binder and Kramer (6); since then the rapid development of RLRP has made it an important surgical alternative for prostatectomy in many countries. In the United States, 60% of prostatectomies were performed with RLRP in 2007 (7). Presently, there are two approaches for RLRP: transperitoneal robot-assisted laparoscopic radical prostatectomy (Tp-RLRP) and extraperitoneal robot-assisted laparoscopic radical prostatectomy (Ep-RLRP).

Although there are some previous comparisons between LRP and RLRP (8-10), the surgical approach was always unclear, like a mixture of transperitoneal and extraperitoneal, data were limited on the comparisons of extraperitoneal LRP (Ep-LRP) vs. Ep-RLRP and Tp-RLRP vs. Ep-RLRP. Therefore, a single-center retrospective analysis was performed in patients diagnosed with localized PC who underwent RLP or LRP from June 2016 to October 2017.

**MATERIALS AND METHODS**

**Patient Selection**

From June 2016 to October 2017, patients diagnosed with organ-confined PC who underwent LPR or RLRP in our institution were included in our study. Patients were excluded from this research if they had had any other malignant tumors and serious diseases. All patients were newly diagnosed and had not received other treatments for PC before, such as brachytherapy, external radiotherapy, chemotherapy, etc. A total of 206 patients were selected into 3 groups (Ep-LRP, Tp-RLRP and Ep-RLRP). Detailed basic characteristics of patients in each group are summarized in Table-1.

**Surgical Technique**

Ep-LRP: Patients were placed in the supine position; five ports were used in the operation. The position for each trocar and general surgical procedures were described previously (11).

Tp-RLRP: Patients were placed in the half lithotomy position with their legs outreached at 30° higher than head level. The position for each trocar and general surgical procedures were described previously (12).

Ep-RLRP group: Unlike the transperitoneal approach, five ports were used lower in the pelvis. The position for each trocar and general surgical procedures were described previously (13).

Laparoscopic technique has been carried out for nearly ten years and robot-assisted operation was developed successfully in our institution based on the mature laparoscopic technique. There was no specific indication for one technique to another, and main influence factors for choosing surgery techniques were patient’s will and figure. Whether transperitoneal or extraperitoneal surgical approach (with or without robotic assistance) were all common surgery styles without learning curve effect.

Patients diagnosed with PC by biopsy underwent surgery at 6-8 weeks after biopsy in order to reduce the difficulty of surgery and postoperative complications. Additionally, patients who underwent transurethral resection of prostate (TURP) should wait 12 weeks for further surgery. All operations were performed by the same surgeon who has worked for 30 years and has been involved in PC surgery. Since 2009, he has completed more than 1,000 cases of LRP (more than 100 cases of RLRP). Additionally, postoperative management for each patient was the same, regardless in LRP or RLRP. In all surgeries, pelvic lymph node dissection (PLND) was performed in patients with a serum prostate specific antigen (PSA) greater than 10 ng/mL, or biopsy
Gleason score (GS) more than 7. In general, the range of PLND includes the nodes covered on external iliac arteries and veins, the nodes within the obturator and the nodes overlying internal and external side of internal iliac arteries (14). Moreover, nerve-sparing procedure was performed according to preoperative evaluation, such as age, tumor clinical grade, magnetic resonance Imaging (MRI) evaluation, International Index of Erectile Function (IIEF) score.

Data extraction

All data analyzed in this study were based on the documentations of our PC database including age, body mass index (BMI), preoperative PSA, biopsy GS, prior history of abdominal surgery, estimated blood loss (EBL), total operation time, postoperative pelvic drainage time, the indwelling catheter time, postoperative length of stay, extra-prostatic extension (EPE), lymph node invasion (LNI) and cases of seminal vesicle and vas deferens involved. The pathological results including postoperative GS and positive surgical margin (PSM) were also documented.

**Statistical analysis**

Stata software (version 12.0; StataCorp LP, College Station, TX) was used for the statistical analysis. Pearson’s chi-square test was used for the comparison of nominal data while the numeric parameters were compared utilizing Student’s t-test. For all analyses, two-sided P value < 0.05 was considered as statistical significant.

**RESULTS**

**Preoperative data**

All operations were completed successfully without conversion. No significant differences in preoperative data were detected between every two groups except the comparison in age between Tp-RLRP and Ep-RLRP which may due to the relatively small sample size (Table-2).
Table 2 - Comparisons in preoperative data between each two groups (Ep-LRP vs Ep-RLRP and Ep-RLRP vs Tp-RLRP).

<table>
<thead>
<tr>
<th></th>
<th>Tp-RLRP</th>
<th>Ep-RLRP</th>
<th>P value</th>
<th>Ep-RLRP</th>
<th>Ep-LRP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), year</td>
<td>70.5±6.23</td>
<td>66.77±7.12</td>
<td>0.0024</td>
<td>66.77±7.12</td>
<td>68.96±7.34</td>
<td>0.0638</td>
</tr>
<tr>
<td>BMI (mean±SD), kg/m²</td>
<td>23.98±2.56</td>
<td>24.19±2.83</td>
<td>0.6599</td>
<td>24.19±2.83</td>
<td>24.06±2.81</td>
<td>0.7761</td>
</tr>
<tr>
<td>Biopsy GS (mean±SD)</td>
<td>7.5±0.75</td>
<td>7.24±0.76</td>
<td>0.0569</td>
<td>7.24±0.76</td>
<td>7.04±0.71</td>
<td>0.0912</td>
</tr>
<tr>
<td>Perioperative PSA (mean±SD), ng/mL</td>
<td>24.51±24.55</td>
<td>24.17±25.72</td>
<td>0.9396</td>
<td>24.17±25.72</td>
<td>26.62±29.74</td>
<td>0.5879</td>
</tr>
<tr>
<td>Clinical T stage, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-T2</td>
<td>38 (70.4%)</td>
<td>63 (80.8%)</td>
<td>0.416</td>
<td>63 (80.8%)</td>
<td>60 (81.1%)</td>
<td>0.951</td>
</tr>
<tr>
<td>T3a</td>
<td>3 (5.6%)</td>
<td>5 (6.4%)</td>
<td>0.838</td>
<td>5 (6.4%)</td>
<td>4 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>11 (20.4%)</td>
<td>8 (10.3%)</td>
<td>0.838</td>
<td>8 (10.3%)</td>
<td>7 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>2 (3.7%)</td>
<td>2 (2.6%)</td>
<td>0.838</td>
<td>2 (2.6%)</td>
<td>3 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>A prior history of abdominal surgery, n (%)</td>
<td>13 (24.1%)</td>
<td>20 (25.6%)</td>
<td>0.838</td>
<td>20 (25.6%)</td>
<td>20 (27.0%)</td>
<td>0.846</td>
</tr>
<tr>
<td>A prior history of TURP, n (%)</td>
<td>3 (5.6%)</td>
<td>5 (6.4%)</td>
<td>0.839</td>
<td>5 (6.4%)</td>
<td>6 (8.1%)</td>
<td>0.686</td>
</tr>
</tbody>
</table>

PSA = prostate specific antigen; GS = Gleason score; Tp-RLRP = transperitoneal robot-assisted laparoscopic radical prostatectomy; Ep-RLRP = extraperitoneal robot-assisted laparoscopic radical prostatectomy; Ep-LRP = extraperitoneal laparoscopic radical prostatectomy; TURP = transurethral resection of prostate; SD = standard deviation

**Perioperative outcome and pathological results**

Detailed information of comparison between each two groups is shown in Table-3. The whole LNI, EPE rate and PSM was 7.3%, 36.4% and 42.2%, respectively.

**Ep-LRP vs. Ep-RLRP**

Longer total operation time [180.45 ± 50.27 vs. 143.80 ± 33.13 min, P = 0.000] was found in Ep-RLRP when compared to Ep-LRP. Additionally, no statistical difference was found in other variables.

**Tp-RLRP vs. Ep-RLRP**

Significant differences were detected in the comparison of EBL [399.07 ± 519.57 vs. 254.49 ± 308.05 mL, P = 0.0473], total operation time [235.98 ± 59.16 vs. 180.45 ± 50.27 min, P = 0.00], postoperative pelvic drainage time [5.37 ± 2.33 vs. 4.24 ± 3.08 d, P = 0.0237] and postoperative length of stay [8.15 ± 3.30 vs. 6.49 ± 3.49 d, P = 0.0068] between Tp-RLRP and Ep-RLRP while difference in the comparisons of other variables showed no statistical significance.

**DISCUSSION**

PC is a male malignant tumor with high incidence (1). Definitive treatment for localized PC includes surgery, radiation therapy, endocrine therapy, active surveillance and watchful waiting. However, radical prostatectomy has been a recognized method for relatively young patients with a life expectancy over 10 years (15). Because of the decreased EBL, shorter length of stay and less postoperative pain that the minimally invasive techniques provide in radical prostatectomy compared to open surgery (16), radical prostatectomy has been always performed in the form of LRP or RLRP in recent years.

There are some typical features favored in RLRP such as 3D viewing, improved ergonomics, elimination of hand tremor and refined dexterity (17, 18), which had made RLRP a good alternative
for radical prostatectomy. However, high cost, lack of training, and reduced budgets of RLRP became the biggest obstacle to its development (19). Similarly, in partial nephrectomy, many studies had shown that robotic-assisted laparoscopic partial nephrectomy is only a viable approach rather than an absolutely better one due to equivalent postoperative outcomes (20) and greater economic burden when compared to laparoscopic partial nephrectomy. Also, some researchers considered RLRP as a product of market profit due to the lack of advanced evidence of surgical advantage (21, 22).

Traditionally, radical prostatectomy can be performed via transperitoneal and extraperitoneal approach. Either a transperitoneal or an extraperitoneal approach have been proved to be safe and effective, and each approach has its advantages and short comes. The main advantages for transperitoneal approach are summarized as following: (1) easier for trocars placement; (2) the larger operation space for procedure, like the placement of a specimen bag and a broader surgical field. However, a steeper Trendelenburg position may lead to upper airway and facial swelling, which may result in worse postoperative recovery (23). The extraperitoneal approach has several advantages: (1) less steep Trendelenburg position can lead to the lower incidence rate of intestinal and peritoneal diseases; (2) Isolation of the operating fields from abdominal cavity can avoid the occurrence of reflex ileus and urinary ascites followed by bleeding to the abdominal cavity (24, 25). However, the risk of injury to the rectum during seminal vesicles dissection increases.

In our study, operation time, postoperative pelvic drainage time, postoperative length of stay, and indwelling catheter time were compared between the two groups (Ep-RLRP vs Ep-LRP and Ep-RLRP vs Tp-RLRP) (Table 3). The results showed that the operation time of Ep-RLRP and Ep-LRP groups were significantly shorter than that of Tp-RLRP group (P < 0.05). The EBL, postoperative length of stay, and postoperative GS were also comparable between the two groups (P > 0.05). However, the indwelling catheter time was significantly shorter in the Ep-RLRP group (P < 0.05). The cases of seminal vesicle involvement were similar between the two groups (P > 0.05). The postoperative pelvic drainage duration time was significantly shorter in the Tp-RLRP group (P < 0.05). The PSM, EPE, PLND, and LNI rate were comparable between the two groups (P > 0.05).

Table 3 - Comparisons in perioperative and pathologically data between each two groups (Ep-RLRP vs Ep-LRP and Ep-RLRP vs Tp-RLRP).

<table>
<thead>
<tr>
<th></th>
<th>Tp-RLRP</th>
<th>Ep-RLRP</th>
<th>P value</th>
<th>Ep-RLRP</th>
<th>P value</th>
<th>Ep-LRP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>operation time (mean±SD), min</td>
<td>235.98±59.16</td>
<td>180.45±50.27</td>
<td>0.000</td>
<td>180.45±50.27</td>
<td>0.000</td>
<td>143.80±33.13</td>
<td>0.000</td>
</tr>
<tr>
<td>EBL (mean±SD), mL</td>
<td>399.07±519.57</td>
<td>254.49±308.05</td>
<td>0.0473</td>
<td>254.49±308.05</td>
<td>0.1433</td>
<td>316.89±200.73</td>
<td>0.4255</td>
</tr>
<tr>
<td>postoperative length of stay (mean±SD), day</td>
<td>8.15±3.30</td>
<td>6.49±3.49</td>
<td>0.0068</td>
<td>6.49±3.49</td>
<td>0.0924</td>
<td>7.09±5.68</td>
<td>0.4255</td>
</tr>
<tr>
<td>the indwelling catheter time, (mean±SD), day</td>
<td>11.52±1.47</td>
<td>11.73±2.88</td>
<td>0.6164</td>
<td>11.73±2.88</td>
<td>0.0924</td>
<td>12.85±5.04</td>
<td>0.0924</td>
</tr>
<tr>
<td>cases of seminal vesicle involved, n (%)</td>
<td>11 (20.4%)</td>
<td>8 (10.3%)</td>
<td>0.104</td>
<td>8 (10.3%)</td>
<td>0.869</td>
<td>7 (9.5%)</td>
<td>0.869</td>
</tr>
<tr>
<td>postoperative pelvic drainage duration time (mean±SD), day</td>
<td>5.37±2.33</td>
<td>4.24±3.08</td>
<td>0.0237</td>
<td>4.24±3.08</td>
<td>0.4705</td>
<td>4.77±5.69</td>
<td>0.4705</td>
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<tr>
<td>PSM, n (%)</td>
<td>19 (35.2%)</td>
<td>34 (43.6%)</td>
<td>0.333</td>
<td>34 (43.6%)</td>
<td>0.770</td>
<td>34 (45.9%)</td>
<td>0.770</td>
</tr>
<tr>
<td>postoperative GS</td>
<td>7.35±0.87</td>
<td>7.35±0.98</td>
<td>0.9726</td>
<td>7.35±0.98</td>
<td>0.4998</td>
<td>7.45±0.83</td>
<td>0.4998</td>
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<tr>
<td>EPE rate, n (%)</td>
<td>13 (24.1%)</td>
<td>30 (38.5%)</td>
<td>0.083</td>
<td>30 (38.5%)</td>
<td>0.549</td>
<td>32 (41.2%)</td>
<td>0.549</td>
</tr>
<tr>
<td>PLND, n (%)</td>
<td>16 (29.6%)</td>
<td>32 (41.0%)</td>
<td>0.178</td>
<td>32 (41.0%)</td>
<td>0.657</td>
<td>33 (44.6%)</td>
<td>0.657</td>
</tr>
<tr>
<td>LNI rate, n (%)</td>
<td>3 (5.6%)</td>
<td>5 (6.4%)</td>
<td>0.840</td>
<td>5 (6.4%)</td>
<td>0.486</td>
<td>7 (9.5%)</td>
<td>0.486</td>
</tr>
</tbody>
</table>

EBL = estimated blood loss; PSM = positive surgical margin; GS = Gleason score; Tp-RLRP = transperitoneal robot-assisted laparoscopic radical prostatectomy; Ep-RLRP = extraperitoneal robot-assisted laparoscopic radical prostatectomy; Ep-LRP = extraperitoneal laparoscopic radical prostatectomy; EPE = extra-prostatic extension; PLND = pelvic lymph node dissection; LNI = lymph node invasion; SD = standard deviation
and less EBL was favored in Ep-RLRP when compared to Tp-RLRP. Comparison between Ep-LRP and Ep-RLRP showed no statistical difference except the longer total operation time in Ep-RLRP.

The operation time, defined as a period of time from the incision of the skin to the end of the skin suture, was different in various surgical approaches. Significant difference (P < 0.0001) between Ep-RLRP and Ep-LRP could have been caused by the extra time for disposition of robot arms. Longer operation time in Tp-RLRP when compared to Ep-RLRP may have occurred due to faster placement of trocars (P < 0.0001).

In terms of EBL, patients with Tp-RLRP had more blood loss than those of Ep-RLRP (399.07 vs. 254.49 mL, P = 0.0473). However, no significant difference was observed in the comparison between Ep-RLRP and Ep-LRP. Therefore, a preliminary conclusion can be drawn that more EBL is tightly associated with the transperitoneal route, similar results can be found in some previous studies which compare EBL between Ep-LRP and Tp-LRP (25-27). One possibility is that a self-made gas bag can make enough pressure on the surrounding tissue to lower the bleeding in extraperitoneal route (28).

In the comparison between Tp-RLRP and Ep-RLRP, we can conclude that the postoperative length of stay and pelvic drainage duration time was significant longer in Tp-RLRP. This might be explained by the disadvantages of Tp-RLRP mentioned above. However, the difference between Ep-LRP and Ep-RLRP showed no statistical significance which indicated that the robot-assisted technique did not have especially obvious effect on postoperative recovery.

Generally, postoperative pathological results were tightly to PSM and postoperative GS. PSM is an independent predictor of tumor progression which can probably be prevented by appropriate patient selection and meticulous surgical technique (29). In our study, no significant differences were observed in PSM and postoperative GS in each two groups. As the results of Hakimi et al. (30) and Eden et al. (11) research, which compared PSM in (LRP vs. RLRP) and (ELRP vs. TLRP), showed no statistical significance in the comparison of PSM. However, the relatively small sample size and the lack of long-term follow-up data of biochemical recurrence limited the evaluation of postoperative conditions; larger sample size and longer follow-up are needed. The relatively high PSM rate (42.23%) in this series should not be ignored. We reviewed the biopsy GS and pre-operative PSA of all patients included and found that most patients were in or above intermediate risk, besides, the extra-prostatic extension rate suggested the similar results in postoperative pathology. Certainly, the small sample size may also have played a role.

In Table-3, we can found that postoperative duration of catheter was relatively long in our instruction and the pelvic drainage is today rarely routinely placed in many centers. Firstly, we attributed the longer duration of catheter to the different concepts we told to patients, what’s mean that we will try to prolong the duration of catheter as slightly as possible (while ensuring no infection) to ensure a better anastomosis between the urethra and the bladder, and to reduce the incidence of anastomotic leakage and urinary failure after extubation. Secondly, there have been many reports on postoperative pelvic drainage and they mentioned that incidence of adverse events in the no drain group was not inferior to the group who received a pelvic drainage (31). However, placement of drainage tubes is a generally accepted concept in China. Additionally, Patel et al. (32) believes that the contents of the drainage tube can provide additional information after surgery, potential bleeding and leakage of urine or serious complications can be detected earlier through the observation of the color and volume of the drainage or the inspection of the drainage if necessary. Moreover, the drainage tube can reduce the formation of postoperative hematoma, and patients with hematoma have long been confirmed to have a large proportion of bladder neck contracture and permanent urinary incontinence (33).

This was a single-instruction, retrospective study, and no strict selection criteria were applied when choosing the surgery technique (almost to be a randomized clinical trial). The surgeon has already been an experienced operator, and we thought the bias of experience accumulation can be minimized. The limitation for this study could be overcome by expanding the number of cases.
CONCLUSIONS

In RLRP, Ep-RLRP was proved to be a safe and effective approach because of the shorter operation time, postoperative pelvic drainage time, postoperative length of stay and less EBL when compared to Tp-RLRP. Ep-RLRP and Ep-LPR provides equivalent perioperative and pathological outcomes.

ABBREVIATIONS

PC = prostate cancer
ORP = open radical prostatectomy
LRP = laparoscopic prostatectomy
RLRP = robot-assisted laparoscopic prostatectomy
Tp-RLRP = transperitoneal robot-assisted laparoscopic radical prostatectomy
Ep-RLRP = extraperitoneal robot-assisted laparoscopic radical prostatectomy
Ep-LPR = extraperitoneal laparoscopic radical prostatectomy
TURP = transurethral resection of prostate
PLND = pelvic lymph node dissection
PSA = prostate specific antigen
GS = Gleason score
MRI = magnetic resonance imaging
IIEF = International Index of Erectile Function
BMI = body mass index
EBL = estimated blood loss
EPE = extra-prostatic extension
LNI = lymph node invasion
PSM = positive surgical margin

CONFLICT OF INTEREST

None declared.

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Factors affecting urinary continence and sexual potency recovery after robotic-assisted radical prostatectomy

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1 Hospital Sírio-Libanês, São Paulo, SP, Brasil; 2 Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brasil

ABSTRACT

Introduction: Robot-assisted radical prostatectomy (RARP) is the most recent surgical technique for localized prostate cancer. The Da Vinci (Intuitive Surgical, Sunnyvale, CA) system was first introduced in Brazil in 2008, with a fast growing number of surgeries performed each year.

Objective: Our primary endpoint is to analyze possible predictors of functional outcomes, related to patient and tumor features. As secondary endpoint, describe functional outcomes (urinary continence and sexual potency) from RARP performed in the Sírio-Libanês Hospital (SLH), a private institution, in São Paulo, from April 2008 to December 2015.

Materials and Method: Data from 104 consecutive patients operated by two surgeons from the SLH (MA and SA) between 2008 and 2015, with a minimum 12 months follow-up, were collected. Patient features (age, body mass index - BMI, PSA, date of surgery and sexual function), tumor features (tumor stage, Gleason and surgical margins) and follow-up data (time to reach urinary continence and sexual potency) were the variables collected at 1, 3, 6 and 12 months and every 6 months thereafter. Continence was defined as the use of no pad on medical interview and sexual potency defined as the capability for vaginal penetration with or without fosphodiesterase type 5 inhibitors.

Results: Mean age was 60 years old and mean BMI was 28.45 kg/m2. BMI >30kg/m2 (p<0.001) and age (p=0.011) were significant predictors for worse sexual potency after surgery. After 1, 3, 6 and 12 months, 20.7%, 45.7%, 60.9% and 71.8% from patients were potent, respectively. The urinary continence was reached in 36.5%, 80.3%, 88.6% and 92.8% after 1, 3, 6 and 12 months, respectively. Until the end of the study, only one patient was incontinent and 20.7% were impotent.

Conclusion: Age was a predictor of urinary and erectile function recovery in 12 months. BMI was significant factor for potency recovery. We obtained in a private hospital good functional results after 12 months of follow-up.

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INTRODUCTION

Prostate cancer is the most common solid organ neoplasm in men and the second cause of cancer death in Brazil. Estimates of the National Cancer Institute (INCA) for the year 2016 predict 61,200 new cases. In 2013, 13,770 deaths by prostate cancer were confirmed (1).
Since Walsh’s nerve sparing technique, radical prostatectomy has become the preferred method for prostate cancer treatment (2). Robot-assisted laparoscopic radical prostatectomy (RARP) was introduced in 2001 and quickly spread in USA. In 2008, the first RARP was performed in Brazil. The benefit of RARP on functional outcomes was demonstrated first by Tewari et al., who reported a faster potency and continence recovery over open radical prostatectomy (3).

Quality of life after surgery is strictly related to continence and potency recovery (4). Therefore, besides cancer control, functional outcomes have been studied in an attempt to understand which patients may be at increased risk. Pre-operative orientation could improve patient satisfaction and quality-of-life. Furthermore, the risk of any sequel discourages many patients and surgeons considering radical prostatectomy.

To our knowledge, there is no national publication reporting predictors of functional outcomes recovery after RARP with more than one hundred patients. The main objective of this study is to analyze predictors of functional outcomes recovery after robot-assisted radical prostatectomy in a private hospital in Brazil.

**MATERIALS AND METHODS**

After approval by the Research Ethics Committee of the Sírio Libanês Hospital, medical and hospital records data were collected from patients submitted to robot-assisted laparoscopic prostatectomy between April 2008 and December 2015 by two surgeons of the Sírio Libanês Hospital (SA. e MA), a private hospital in São Paulo, Brazil.

All patients have been diagnosed with adenocarcinoma of the prostate by biopsy of the prostate guided by transrectal ultrasonography with at least 12 fragments. Only patients with clinically localized disease, life expectancy greater than 10 years and postoperative follow-up of at least 12 months, were included. Patients with previous history of radiotherapy or any neoadjuvant therapy were excluded.

The data collected were age, body mass index (BMI), sexual function prior to the procedure (by interview), PSA (ng/dL, at the time of diagnosis), prostate size – weighing of the piece performed by the pathologist (grams), date of surgery, comorbidities (hypertension, dyslipidemia, diabetes and smoking; based on the use of medications and previous medical history), Gleason of the surgical piece, pathological stage (2002 TNM of the American Joint Committee on Cancer/Union for International Cancer Control), (5) sexual potency recovery time (weeks; defined as the capacity for vaginal penetration, with or without the use of phosphodiesterase-5 inhibitors) and urinary continence (weeks; defined as the full continence capacity, without the use of absorbents).

Surgeries were performed according to the technique described by Patel (6). Most of the time, Rocco’s point and bilateral nerve sparing (BNS) were performed when possible. Patients with a suspicious capsule invasion in either side of the prostate were usually not submitted to the BNS, in order to prevent positive surgical margin. The patient was discharged 2 to 3 days after the procedure and the bladder catheter was removed on the 10th postoperative day. Patients were instructed by the surgeons on sphincter rehabilitation the day the catheter was removed and we stimulated the use of iPD-5 for all patients after the first post-operative month, either with tadalafil 5mg on a daily basis, or sildenafil 50mg three times a week.

**Statistical analysis**

Continuous quantitative variables were described by measures of central tendency and dispersion, while categorical variables were described by means of absolute and relative frequencies (percentages).

The time to reach potency and continence was assessed through Kaplan-Meier. The comparison of the curves was done by the log-rank test for categorical variables. Patients who did not reach potency / continence according to the pre-established criteria (see methods), until the last consultation, were considered impotent and incontinent.

Cox regression models were constructed to identify independent predictors of urinary continence and sexual potency for continuous variables. Only the variables that reached p<0.25 in the analysis were included in the multivariate analysis.
The results of the statistical tests were considered significant when \( p < 0.05 \). All variables were entered into a database and analyzed using the R statistical program (R Core Team, 2014).

**RESULTS**

Between 2008 and 2016, 104 consecutive robot-assisted laparoscopic radical prostatectomies were performed at the Sírio Libanês Hospital by surgeons SA and MA. The average age was 60 years (35-80 years) and the average BMI was of 28.45 kg/m\(^2\) (±4.2 kg/m\(^2\)). The remaining descriptive (Table-1) and categorical (Table-2) characteristics of the series of patients are described below.

Data from 96 and 94 patients were analyzed for continence and potency, respectively. Two patients did not return to all the scheduled appointments and 6 patients had important data missing from their charts. Another 2 patients were excluded from potency analysis as they started androgen deprivation therapy (ADT) before 6 months of follow-up.

None of the analyzed continuous variables (BMI, PSA, D’Amico risk, presence of positive margins, prostate volume, BNS, age and comorbidities) were shown to be related to continence recovery in the univariate analysis (Table-3). However, when age was analyzed as a categorical variable (>60 years old), it was significant \( (p = 0.03) \).

In the univariate analysis, BMI \( (p < 0.001) \) and age \( (p = 0.11) \) were statistically significant factors that influenced potency recovery. They also remained statistically significant in the multivariate analysis. Figure-1 illustrates the likelihood of remaining impotent according to BMI over time. After 24 months, no patient with BMI >30 kg/m\(^2\) regained sexual potency.

Hypertension, diabetes, smoking, dyslipidemia and the presence of comorbidities also did not influence the recovery of sexual potency. The evaluation of age as a categorical variable wasn’t statistically significant.

The frequency of continent patients immediately after removal of the bladder catheter and after 3, 6 and 12 months were of 36.5%; 80.3%; 88.6% and 92.8%, respectively. After the first year, 6 patients who were incontinent (6.2%) recovered urinary continence by the end of the evaluated period (Table-4). Figure-2 shows the evolution of urinary continence recovery over time. The average time for continence recovery was 2.66 months.

Recovery of sexual potency occurred as early as the first month for 20.7% of patients. In the course of 3, 6 and 12 months, 45.7%; 60.9% and 71.8% recovered potency, respectively (Table-4 and Figure-3). The average time to recover sexual potency was 7.72 months. Nineteen patients (20.7%) remained impotent.

**DISCUSSION**

Urinary incontinence is considered the complication that most affects the patient’s quality of life. After the first year of follow-up, more than 90% of the patients were continent \((\text{no pad})\) in this series. The average time for continence recovery was 2.66 months. Our continence results, at the end of the first year after surgery, are within the range observed in the systematic review and meta-analysis of Ficarra et al., which showed an average incidence of urinary incontinence at 12 months of 9% (8%-11%), despite considering continent patients using up to 1 pad per day (8). Another multi-institutional study with 1,812 patients showed incontinence rates of 21% (considering 0 pad) after 12 months (9). The number of patients

| Table 1 - Descriptive summary of continuous characteristics. |
|-----------------|-----|-----|-----|-----|-----|-----|
|                | N   | Min | Median | Max | Mean | SD  |
| Age            | 104 | 35  | 61    | 80  | 60.05 | 8.34 |
| BMI            | 62  | 19.08 | 28.39 | 42.93 | 28.45 | 4.2  |
| PSA            | 103 | 0.88 | 5.6   | 41  | 6.48  | 4.67 |

\( N = \text{Sample size}; \ SD = \text{Standard Deviation} \)
who reached urinary continence immediately after the withdrawal of the bladder catheter (36.5%) was also in agreement with the literature, which varies from 13.1% - 68.9% (3, 10, 11).

We chose to include in the study patients with a minimum of 12 months of follow-up, since it is the period in which most patients recover sexual function and urinary continence. Some patients in the present study regained urinary continence after more than 2 years of follow-up. In a series by Ficarra et al., there was no continence recovery after 12 months (12), although another study showed that a slow recovery may be the case (13).

Among the possible predictors of urinary continence that have been reported (age, obesity, length of the membranous urethra, anastomotic stricture, experience of the surgeon, neurovascular bundle preservation, large prostate volume,

Table 2 - Descriptive summary of categorical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Quantity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (Kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>46</td>
<td>74.2</td>
</tr>
<tr>
<td>&gt;30</td>
<td>16</td>
<td>25.8</td>
</tr>
<tr>
<td><strong>PSA (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>90</td>
<td>87.4</td>
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<tr>
<td>10-20</td>
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<td>10.7</td>
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<td>&gt;20</td>
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<td>7</td>
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<td>8-9</td>
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<td>Extensive Impairment</td>
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<td>With Unilateral Preservation</td>
<td>24</td>
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<td>With Bilateral Preservation</td>
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<td><strong>Pathological Stage</strong></td>
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<td>pT2</td>
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<td>75</td>
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<tr>
<td>pT3</td>
<td>26</td>
<td>25</td>
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Table 3 – Descriptive data according to continence and potency status.

<table>
<thead>
<tr>
<th></th>
<th>Incontinence</th>
<th>Impotence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quantity/Total (%)</td>
<td>Quantity/Total (%)</td>
</tr>
<tr>
<td><strong>BMI (Kg/m²)</strong></td>
<td>p=0.294</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>&lt;30</td>
<td>3/45 (6.7)</td>
<td>35/43 (81.4)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>3/15 (20)</td>
<td>6/15 (40)</td>
</tr>
<tr>
<td><strong>PSA (mg/dL)</strong></td>
<td>p=0.91</td>
<td>p=0.229</td>
</tr>
<tr>
<td>&lt;10</td>
<td>7/85 (8.2)</td>
<td>60/84 (71.4)</td>
</tr>
<tr>
<td>10-20</td>
<td>2/11 (18.2)</td>
<td>6/9 (66.7)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>0/2 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td><strong>Gleason Sum</strong></td>
<td>p=0.355</td>
<td>p=0.976</td>
</tr>
<tr>
<td>6</td>
<td>1/16 (6.2)</td>
<td>12/15 (80)</td>
</tr>
<tr>
<td>7</td>
<td>5/60 (8.3)</td>
<td>42/60 (70)</td>
</tr>
<tr>
<td>8-9</td>
<td>3/23 (13)</td>
<td>13/21 (61.9)</td>
</tr>
<tr>
<td><strong>Margins</strong></td>
<td>p=0.431</td>
<td>p=0.48</td>
</tr>
<tr>
<td>Negative</td>
<td>7/85 (8.2)</td>
<td>62/82 (75.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>2/14 (14.3)</td>
<td>5/14 (35.7)</td>
</tr>
<tr>
<td><strong>Extra-prostatic extension</strong></td>
<td>p=0.454</td>
<td>p=0.676</td>
</tr>
<tr>
<td>No extension</td>
<td>6/76 (7.9)</td>
<td>54/73 (74)</td>
</tr>
<tr>
<td>Focal extension</td>
<td>2/20 (10)</td>
<td>13/21 (61.9)</td>
</tr>
<tr>
<td>Larger extension</td>
<td>1/3 (33.3)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td><strong>Seminal Vesicles</strong></td>
<td>p=0.404</td>
<td>p=0.815</td>
</tr>
<tr>
<td>Negative</td>
<td>8/92 (8.7)</td>
<td>63/90 (70)</td>
</tr>
<tr>
<td>Positive</td>
<td>1/6 (16.7)</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td><strong>Neurovascular Bundles</strong></td>
<td>p=0.678</td>
<td>p=0.145</td>
</tr>
<tr>
<td>No preservation</td>
<td>0/4 (0)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>Unilateral preservation</td>
<td>3/20 (15)</td>
<td>11/20 (55)</td>
</tr>
<tr>
<td>Bilateral preservation</td>
<td>6/55 (10.9)</td>
<td>41/54 (75.9)</td>
</tr>
<tr>
<td><strong>Pathologic stage</strong></td>
<td>p=0.8</td>
<td>p=0.75</td>
</tr>
<tr>
<td>pT2</td>
<td>6/76 (7.9)</td>
<td>54/73 (74)</td>
</tr>
<tr>
<td>pT3</td>
<td>3/23 (13)</td>
<td>13/23 (56.5)</td>
</tr>
</tbody>
</table>
obstructive urinary symptoms and the preservation of the bladder neck) (14), age is one of the most consistent (15). Most published series have shown that young patients (<60 years old) present faster recovery and better results in 12 months (16-19). Lavigueur-Blouin et al. evaluated the predictive factors for early recovery (up to 1 month) of continence after RARP, where 57% of patients younger than 55 years of age were continent in the first month and only 33% of patients with more advanced age (20). In our series, age as a categorical variable (≤60 years old and >60 years old) was also a predictor of continence.

Obesity (BMI ≥30 kg/m²) has also been reported as an adverse prognostic factor in radical prostatectomy. In a recent review study, BMI was responsible for longer surgical time, greater surgical bleeding and worse functional results (21). Wiltz et al. published one of the largest series, with 945 patients stratified using BMI into normal (<25 kg/m²), overweight (≥25 and <30 kg/m²) and obese (≥30 kg/m²) (13). Patients with normal BMI presented better continence results compared to more obese patients after 12 months (70% vs. 68% vs. 57%, p=0.03) and 24 months (75% vs. 71% vs. 57%, p=0.04). Ahlering et al. also reported worse results for obese patients, being 47% of patients with BMI≥30 kg/m² continent (0 pad) after 6 months (p≤0.001) (22). In our series, 16 patients presented BMI ≥30 kg/m² at the time of surgery (15 with complete data), and there was no statistical difference in recovery of urinary continence compared to patients with BMI <30 kg/m². Although it did not reach statistical significance, we observed that the average time to reach urinary continence was almost double for obese patients (5.08 months vs. 2.71 months). This may be explained due to the small number of obese patients in the series.

After 1, 3, 6 and 12 months, there were 20.7%, 45.7%, 60.9% and 71.8% of patients who recovered sexual potency, respectively. In 19 cases (20.7%) there was no recovery of sexual function. The average time to recover sexual potency was 7.72 months. Shikanov et al. reported similar results using the interview made by the surgeon. After 3, 6 and 12 months, results were 57%, 63% and 82%, respectively (23). Using SHIM (Sexual Health Index for Men) questionnaire, a Canadian study with 722 cases reported recovery of sexual potency in 1, 3, 6 and 12 months of 19.5%; 31.4%; 37.2% and 52.4% (24).

The relationship between BMI and sexual potency recovery after RARP is suggested in some

Figure 1 – Estimates of the probability of impotence considering BMI - Kaplan Meier Estimates.
studies, but it is still controversial (25, 26). It is intuitive that the presence of a greater amount of periprostatic adipose tissue may increase the chance of injury to the neurovascular bundle. Obesity is also associated with the metabolic syndrome, the use of medications that may affect the quality of the erection, in addition to an endothelial inflammation and dysfunction (27). In the series of Wiltz et al. the results were significantly worse after RARP for obese patients when compared to overweight

Table 4 – Recovery of urinary continence and sexual potency.

<table>
<thead>
<tr>
<th>Time to urinary continence recovery</th>
<th>Number</th>
<th>Absolute percentage (%)</th>
<th>Acumulated percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>35</td>
<td>36.5</td>
<td>36.5</td>
</tr>
<tr>
<td>3 months</td>
<td>42</td>
<td>43.8</td>
<td>80.3</td>
</tr>
<tr>
<td>6 months</td>
<td>8</td>
<td>8.3</td>
<td>88.6</td>
</tr>
<tr>
<td>12 months</td>
<td>4</td>
<td>4.2</td>
<td>92.8</td>
</tr>
<tr>
<td>Over 12 months</td>
<td>6</td>
<td>6.2</td>
<td>99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to sexual potency recovery</th>
<th>Number</th>
<th>Absolute percentage (%)</th>
<th>Acumulated percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>19</td>
<td>20.7</td>
<td>20.7</td>
</tr>
<tr>
<td>3 months</td>
<td>23</td>
<td>25</td>
<td>45.7</td>
</tr>
<tr>
<td>6 months</td>
<td>14</td>
<td>15.2</td>
<td>60.9</td>
</tr>
<tr>
<td>12 months</td>
<td>10</td>
<td>10.9</td>
<td>71.8</td>
</tr>
<tr>
<td>Over 12 months</td>
<td>7</td>
<td>7.6</td>
<td>79.4</td>
</tr>
<tr>
<td>No recovery</td>
<td>19</td>
<td>20.7</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 2 – Relation of percentage of continent patients with time (months).
Figure 3 – Percentage of potent patients over time (months).

(BMI \geq 25 \text{kg/m}^2 \text{ and } <30 \text{kg/m}^2) \text{ and normal patients (BMI}<25\text{kg/m}^2), \text{ with 48.4\%, 59.6\% and 68.5\% of potent patients after 12 months, and 55.9\%, 78.9\% and 80.3\% after 24 months, respectively (p=0.02) (13). Wiltz et al. analysis considered only bilateral bundle preservation surgeries (13). The association between BMI \geq 30 \text{kg/m}^2 \text{ and erectile dysfunction 12 months after RARP (p<0.001) found in our study may be related to the prior committed sexual function and the presence of other comorbidities that were not evaluated.}

The association between comorbidities that increase cardiovascular risk such as diabetes, hypertension, dyslipidemia, and smoking with erectile dysfunction is well recognized (28). Such diseases could also influence the recovery of sexual potency after RARP (29). Isolated comorbidities or the presence of any of them (hypertension, diabetes, dyslipidemia and smoking history) were not significant for the recovery of both potency and urinary continence. It is important to emphasize that we considered smokers all patients with previous or current or smoking history and we did not quantify packs consumed per year and time.

Our study presents a number of limitations inherent to a retrospective study. Data collected from medical and hospital records are not always complete and often underestimate complications and eventually overestimate the results. No specific urinary continence or sexual potency questionnaires were applied, which could provide more reliable data. Nevertheless, since we considered continent all patients who did not need any type of pad protection, we believe that the results were not significantly influenced by the absence of a specific questionnaire. Accordingly, we defined as potent those patients who had sexual intercources with or without the aid of phosphodiesterase–5 blocking drugs. We believe that this also reduced the impact of the absence of a specific questionnaire regarding sexual potency. This is a pioneer study, as it comes from a private hospital in Brazil with no residence or fellow programs, analyzing a fairly recent technique that is not accessible to the majority of the patient and medical population. To our knowledge, this is also the first study reporting predictors of functional outcome recovery after RARP with more than one hundred patients.

CONCLUSIONS

Age and obesity influenced the recovery of sexual potency, while only age was related to the recovery of urinary continence. We obtained good functional results, within the range of the largest published series, despite still within the learning
curve. Prospective national studies with a larger number of patients are needed to better analyze functional results in larger Brazilian series.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Fax: + 55 11 3255-4145
E-mail: marcoarap@hotmail.com
Detection of clinically significant prostate cancer with PI-RADS v2 scores, PSA density, and ADC values in regions with and without mpMRI visible lesions

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ABSTRACT

Purpose: To determine if PSAD, PSADtz, and ADC values improve the accuracy of PI-RADS v2 and identify men whose concurrent systematic biopsy detects clinically significant cancer on areas without mpMRI visible lesions.

Materials and methods: Single reference-center, cross-sectional, retrospective study of consecutive men with suspected or known low to intermediate-risk prostate cancer who underwent 3T mpMRI and TRUS-MRI fusion biopsy from 07/15/2014 to 02/17/2018. Cluster-corrected logistic regression analyses were utilized to predict clinically significant prostate cancer (Gleason score ≥3+4) at targeted mpMRI lesions and on systematic biopsy.

Results: 538 men (median age=66 years, median PSA=7.0ng/mL) with 780 mpMRI lesions were included. Clinically significant disease was diagnosed in 371 men. PI-RADS v2 scores of 3, 4, and 5 were clinically significant cancer in 8.0% (16/201), 22.8% (90/395), and 59.2% (109/184). ADC values, PSAD, and PI-RADS v2 scores were independent predictors of clinically significant cancer in targeted lesions (OR 2.25-8.78; P values <0.05; AUROC 0.84, 95% CI 0.81-0.87). Increases in PSAD were also associated with upgrade on systematic biopsy (OR 2.39-2.48; P values <0.05; AUROC 0.69, 95% CI 0.64-0.73).

Conclusions: ADC values and PSAD improve characterization of PI-RADS v2 score 4 or 5 lesions. Upgraded on systematic biopsy is slightly more likely with PSAD ≥0.15 and multiple small PI-RADS v2 score 3 or 4 lesions.
volumes estimated using transrectal ultrasound (TRUS), to improve the prediction of cancer grade in men with low and intermediate total serum PSA range (4, 5), but little data has been produced since the advent of mpMRI.

The interpretation of continuous variables, especially those with a large number of possible values, e.g. PSAD, PSADtz, and ADC values, is not simple. An approach that simplifies the use of such results in clinical practice is stratification into categories that represent different risks of an outcome. This strategy is often utilized; for example, PI-RADS states that lesions with ADC values below 750 to 900 × 10^{-6}mm^2/s are more likely to represent prostate cancer (1). And a PSAD of greater than 0.15 has been shown to be associated with a higher rate of Gleason ≥3+4 disease in patients with a positive mpMRI (2). Although the incorporation of these strategies has been suggested, further validation is required.

Concurrent systematic biopsies are performed in the vast majority of men who undergo TRUS-MRI fusion biopsy. This is because PI-RADS v2 scores do not adequately predict the identification of clinically significant prostate cancer in regions sampled on systematic biopsy that are negative on mpMRI (6, 7). For increased clarity, perhaps we could modify this paragraph slightly as suggested below.

PSAD, PSADtz, and ADC values may help to identify which men with visible lesions on mpMRI have a higher risk of having a clinically significant tumor detected on conventional systematic biopsy. If so, the combined procedure could be reserved for those men. Other patients could undergo targeted TRUS-MRI fusion biopsy only and avoid the unnecessary sampling.

Accordingly, the goals of this study are to determine if PSAD, PSADtz, and ADC values improve the accuracy of PI-RADS v2 and identify men whose concurrent systematic biopsy detects clinically significant cancer on areas without mpMRI visible lesions.

MATERIALS AND METHODS

This is a retrospective single institution study, approved by the institutional review board, and compliant with the United States Health Insurance Portability and Accountability Act of 1996. Informed consent was waived.

Population

All consecutive men with suspected or known low to intermediate-grade prostate cancer who underwent mpMRI from 07/15/2014 to 02/17/2018, followed by a TRUS-MRI fusion biopsy, were eligible.

Inclusion criteria

- If known cancer, Gleason scores 3+3 or 3+4
- 3-Tesla endorectal mpMRI
- PI-RADS v2 scores 3 to 5

Exclusion criteria

- Men without focal abnormalities on mpMRI (PI-RADS v2 scores 1 or 2)
- Patients submitted to TRUS-guided systemic biopsy alone, without MRI-fusion biopsy
- Non-retrievable clinical, imaging, or pathological data
- Artifact precluding imaging interpretation

Men without focal abnormalities on mpMRI, i.e. those who were assigned a PI-RADS scores 1 or 2, were not included in this study because these patients undergo systematic TRUS-guided biopsy, rather than TRUS-MRI fusion biopsy.

Data collection

Patients were identified through a search of imaging reports using Nuance mPower Clinical Analytics® (Nuance Communications, Inc. Burlington, Massachusetts). Our standardized report allowed us to find all scans done within the time frame using the key word “PI-RADS v2”. Additional data was obtained from our electronic radiology and medical records. Two authors collected all data. A third author performed a QA review of a random sample of the data.

The following data were acquired: age, race/ethnicity, family history of prostate cancer, baseline PSA, presence of palpable nodule, history
and results of previous biopsy (none, benign, positive, and highest Gleason score), mpMRI prostate volume, mpMRI volume of the transition zone, number of lesions on mpMRI, lesion mpMRI characteristics (peripheral or transition zone, PI-RADS v2 score, three-plane diameters, volume, mean ADC value), lesion Gleason scores obtained with TRUS-MRI fusion biopsy, and highest Gleason score on systematic biopsy. PSAD and PSADtz were calculated dividing the baseline total serum PSA value by the prostate volume and transition zone volume, respectively (4, 5).

MRI protocol

Images were acquired on a 3-Tesla magnet (Discovery™ MR750 or Discovery™ MR750w GEM (GE Healthcare LLC, Arlington Heights, IL) using an endorectal coil (MEDRAD® Prostate eCoil, Bayer HealthCare LLC, Whippany, NJ). The protocol followed the PI-RADS v2 guidelines and included high-resolution T2-weighted images, high b-value diffusion-weighted images, and dynamic contrast-enhanced images (1). Details are provided in Appendix 1.

Interpretation

Scans were interpreted by one of 13 board-certified, fellowship-trained, abdominal radiologists as part of clinical care. Approximately 75% of cases were interpreted by one of 5 radiologists, one of whom reviewed one third of the cases and the others approximately 10% each. Images were evaluated according to PI-RADS v2 and suspicious findings assigned a score 3 or higher (1). Up to 4 lesions were identified per patient. Mean ADC values were measured at a single slice depicting the most suspicious area of the lesion. Regions-of-interest were drawn to cover between 50% and 75% of the diameter of the lesion, as is customary at our institution (Figure-1). The gland and lesions were outline in DynaCAD for Prostate® (Invivo, Gainesville, FL, USA) for subsequent TRUS-MRI fusion biopsy.

TRUS-MRI fusion biopsies

TRUS-MRI fusion biopsies were performed by subspecialized urologists as part of clinical care using UroNav Fusion Biopsy System® (Invivo,
Gainesville, FL, USA) and 18-gauge needles. Based on the size of the target, one or two samples were taken from the center of the lesion and one or two cores from its periphery. This was followed by a 14-core extended-sextant systematic biopsy. Targeted and systematic biopsies were performed during the same session, by the same urologist. One of 4 urologists performed all procedures, but over 95% of these were done by two urologists with more than 2 years of experience with TRUS-MRI fusion biopsy.

Histological analysis
Specimens were fixed on formalin and H&E stained; immunohistochemistry was performed when deemed necessary by the pathologist. Subspecialized genitourinary pathologists (experience ranging from 3 years to 18 years) interpreted the specimens using the International Society of Urological Pathology guidelines. Targeted and systematic samples were identified separately.

Statistical analysis
Histopathology results were the standard of reference. According to the PI-RADS v2 guidelines (1), our outcome was clinically significant prostate cancer, defined as a Gleason score ≥3+4. The units of analyses were a) the individual mpMRI lesion and b) individual patient upgrade on systematic biopsy. Upgrade on systematic biopsy was defined as the identification of a tumor on systematic biopsy with a Gleason score of at least 3+4 and higher than the Gleason score of the targeted lesions.

Logistic regression analyses were utilized to predict clinically significant prostate cancer at targeted mpMRI lesions and to predict upgrade. Analyses were cluster-corrected to account for the possibility of more than one lesion per patient. Forward and backward selection were utilized to identify variables for inclusion in the multivariate models. ADC values were categorized into four groups, high (above 1100×10⁻⁶mm²/s), mildly low (between 1100 and 900×10⁻⁶mm²/s), moderately low (between 900 and 750×10⁻⁶mm²/s), and markedly low (below 750×10⁻⁶mm²/s). These cutoff values were chosen based on the suggestions of PIRADS and previous publications (1, 8). PSAD was similarly stratified in four categories: low (less than 0.15ng/mL/mL), mildly high (between 0.15 and 0.20ng/mL/mL), moderately high (between 0.20 and 0.25ng/mL/mL), and markedly high (above 0.25ng/mL/mL). We made this option because 0.15ng/mL/mL is a commonly used threshold in urology, and followed this by 0.5 increments. The area under the receiver-operating characteristic (ROC) curves were estimated and bootstrapping used to calculate 95% confidence intervals. We tested the equality of ROC curves utilizing the roccomp routine. Analyses were performed using Stata 13.1® (StataCorp LP, College Station, TX, U.S.A.). All tests were two-tailed and a 5% level of confidence was considered significant.

RESULTS

Demographics
761 men were eligible to this study, but after applying the inclusion and exclusion criteria, 538 were included. 198 (36.8%) were biopsy-näive, 55 (10.2%) had a prior negative biopsy, and 285 (53.0%) were under active surveillance. The median age and baseline PSA were 66 years (IQR=61-70) and 7.0ng/mL (IQR=5.5-9.8). The median interval between mpMRI and biopsy was 57 days (IQR=27-112). Table-1 provides further detail.

PSAD and Imaging Findings
Table-1 also displays the imaging findings, PSAD, and PSADtz of the sample. The median prostate and transition zone volumes were 50.0cm³ (IQR=37.0-74.0) and 26.0cm³ (IQR=14.5-47.8). 780 PI-RADS v2 score 3 to 5 lesions were identified on mpMRI; 780 PI-RADS v2 score 3 to 5 lesions were identified on mpMRI; most were in the peripheral zone (625/780, 80.1%).

Biopsy
Gleason score ≥3+4 was diagnosed in PI-RADS v2 scores of 3, 4, and 5 in 8.0% (16/201), 22.8% (90/395), and 59.2% (109/184) of lesions (Table-2).
Table 1 - Baseline characteristics and imaging findings.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong> *</td>
<td>66 (61-70)</td>
<td></td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong> **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American indian or Alaska native</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>35 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Black/african-american</td>
<td>19 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or latino</td>
<td>20 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Native hawaiian or another pacific island</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>White/caucasian</td>
<td>428 (79.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>34 (6.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of prostate cancer</strong> **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>136 (25.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>402 (74.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Palpable nodule on DRE</strong> **</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (10.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>480 (89.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Biopsy prior to MRI</strong> **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>198 (36.8)</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>55 (10.2)</td>
<td></td>
</tr>
<tr>
<td>3+3</td>
<td>234 (43.5)</td>
<td></td>
</tr>
<tr>
<td>3+4</td>
<td>51 (9.5)</td>
<td></td>
</tr>
<tr>
<td>**Baseline PSA (ng/mL) *</td>
<td>7 (5.5-9.9)</td>
<td></td>
</tr>
<tr>
<td>**Prostate volume (cm³) *</td>
<td>50.0 (37.0-74.0)</td>
<td></td>
</tr>
<tr>
<td>**Transition zone volume (cm³) *</td>
<td>26.0 (14.5-47.8)</td>
<td></td>
</tr>
<tr>
<td>**PSA density *</td>
<td>0.14 (0.10-0.21)</td>
<td></td>
</tr>
<tr>
<td><strong>PSA density categorical</strong> **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt; 0.15)</td>
<td>295 (54.8)</td>
<td></td>
</tr>
<tr>
<td>Mildly high (0.15-0.20)</td>
<td>82 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Moderately high (0.20-0.25)</td>
<td>69 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Markedly high (≥ 0.25)</td>
<td>92 (17.1)</td>
<td></td>
</tr>
<tr>
<td>**Transition zone adjusted PSA density *</td>
<td>0.28 (0.16-0.51)</td>
<td></td>
</tr>
<tr>
<td>**PI-RADS v2 scores (peripheral zone) **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>159 (25.4)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>343 (54.9)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>123 (19.7)</td>
<td></td>
</tr>
<tr>
<td>**PI-RADS v2 scores (transition zone) **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>42 (27.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>52 (33.6)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>61 (39.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of lesions/patient</strong> **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>335 (62.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>167 (31.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>29 (5.4)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7 (1.3)</td>
<td></td>
</tr>
<tr>
<td>**Lesion maximum diameter (cm) *</td>
<td>1.3 (0.9 to 1.7)</td>
<td></td>
</tr>
<tr>
<td>**Lesion volume (cm³) *</td>
<td>0.32 (0.14 to 0.71)</td>
<td></td>
</tr>
<tr>
<td>**ADC values (× 10⁻⁶ mm²/s) *</td>
<td>1004 (287.7)</td>
<td></td>
</tr>
<tr>
<td><strong>ADC categorical</strong> **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low (≤ 750)</td>
<td>114 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Low (750-900)</td>
<td>131 (24.4)</td>
<td></td>
</tr>
<tr>
<td>High (900-1100)</td>
<td>120 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Very high (≥ 1100)</td>
<td>168 (31.2)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>5 (0.9)</td>
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</tbody>
</table>

*DRE = digital rectal examination; PSA = prostate specific antigen; MRI = magnetic resonance imaging; PI-RADS v2 = Prostate Imaging Reporting and Data System, version 2; ADC = apparent diffusion coefficient; * = median (interquartile range); ** = count (percentage)
Clinically significant prostate cancer was diagnosed in 371 men (69.0%, 371/538). Targeted biopsy identified 38 of these men (10.2%, 38/371); systematic biopsy, 157 (42.3%, 157/371), and both approaches, 176 (47.4%, 176/371).

Of the 157 men with clinically significant disease detected only on systematic biopsy, 56 were biopsy-naive patients (35.7%; negative mpMRI targets=31; Gleason 3+3 on targets=25). Ten had prior negative biopsy (6.4%; negative mpMRI targets=8; Gleason 3+3 on targets=2). And 91 were men under active surveillance (58.0%; negative mpMRI targets=48; Gleason 3+3 on targets=43).

Logistic Regression-Targeted mpMRI Lesions

Only age, palpable nodule, PI-RADS v2 score, and categorical ADC were identified by both forward and backward selection models to be included in the multivariate models. Additionally, the multivariate models included PSAD, categorical PSAD, or PSADtz. Table-3 summarizes these results. The area under the ROC curve of the multivariate model was 69% (95% CI=64-73) (Figure-3).

DISCUSSION

Our results show that PSAD and ADC values independently improve the PI-RADS v2 prediction of Gleason score ≥3+4 prostate cancer, and that utilizing their categorical versions is likely to have the same clinical impact. Also, adjustment of PSAD to the volume of the transition zone does not seem to provide additional information.

These results corroborate those of Jordan et al. (2), who found that ADC values below...
## Table 3 - Targeted lesion – logistic regression analyses.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>P</th>
<th>95% CI</th>
<th>95% CI</th>
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<td>4</td>
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<td>9.24</td>
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<td>AUROC = 0.74 (95% CI = 0.70-0.77)</td>
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</tr>
<tr>
<td><strong>PI-RADS v2 and ADC</strong></td>
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<td></td>
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<td>4</td>
<td>2.18</td>
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<td>1.18</td>
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<td>0.997</td>
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<td></td>
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<td></td>
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<tr>
<td><strong>PI-RADS v2</strong></td>
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<td></td>
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<td></td>
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<td>7.79</td>
</tr>
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<td>10.59</td>
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<td>5.85</td>
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<td>AUROC = 0.79 (95% CI = 0.74-0.82)</td>
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<td><strong>PI-RADS v2 and PSAD</strong></td>
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<tr>
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<td>6.25</td>
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<tr>
<td>5</td>
<td>15.02</td>
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<td>PSAD categories</td>
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<td></td>
<td></td>
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<td>AUROC = 0.80 (95% CI = 0.75-0.82)</td>
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<td><strong>PI-RADS v2 and PSADtz</strong></td>
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<td><strong>PI-RADS v2, PSAD categories, and ADC categories</strong></td>
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<td></td>
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<td>4</td>
<td>2.25</td>
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</tr>
<tr>
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<td>6.58</td>
<td>&lt;0.001</td>
<td>3.52</td>
<td>12.31</td>
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<td>PSAD categories</td>
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<tr>
<td>2</td>
<td>2.48</td>
<td>0.002</td>
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<td>3.67</td>
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<td>6.10</td>
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<td>2</td>
<td>1.77</td>
<td>0.07</td>
<td>0.95</td>
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<tr>
<td>3</td>
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<td>6.52</td>
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<td>4</td>
<td>8.78</td>
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<td>16.20</td>
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<tr>
<td>AUROC = 0.83 (95% CI = 0.79-0.86)</td>
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<td><strong>PI-RADS v2, PSAD categories, ADC categories, age, and palpable nodule</strong></td>
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<td>PI-RADS v2</td>
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<td>1.18</td>
<td>3.95</td>
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<td>11.58</td>
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<td>PSAD categories</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.46</td>
<td>0.003</td>
<td>1.36</td>
<td>4.46</td>
</tr>
<tr>
<td>3</td>
<td>2.21</td>
<td>0.01</td>
<td>1.20</td>
<td>4.07</td>
</tr>
<tr>
<td>4</td>
<td>3.75</td>
<td>&lt;0.001</td>
<td>2.25</td>
<td>6.25</td>
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<tr>
<td>ADC categories</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>1.76</td>
<td>0.07</td>
<td>0.95</td>
<td>3.23</td>
</tr>
<tr>
<td>3</td>
<td>3.46</td>
<td>&lt;0.001</td>
<td>1.96</td>
<td>6.13</td>
</tr>
<tr>
<td>4</td>
<td>7.73</td>
<td>&lt;0.001</td>
<td>4.18</td>
<td>14.3</td>
</tr>
</tbody>
</table>

P = probability; CI = confidence interval; PI-RADS v2 = Prostate Imaging Reporting and Data System, version 2; AUROC = area under the receiver-operating characteristic curve; PSAD = prostate-specific antigen density; tz = transition zone; ADC = apparent diffusion coefficient.
800x10^{-6}\text{mm}^2/\text{s} improved the characterization PI-RADS v2 score 4 lesions in a population of men seen in a community clinic. More recently, Gaur et al. found that mean ADC values and normalized ADC helped to characterize lesions assigned a PI-RADS v2 score 4 or 5 (9). The authors did not categorize ADC values, but their ROC analysis suggested that a 1050x10^{-6}\text{mm}^2/\text{s} mean ADC value threshold increases the diagnostic accuracy of PI-RADS v2. This number is within our category of mildly low ADC values that were associated with at least doubling of the odds of clinically significant prostate cancer. Lin et al., however, did not identify an improvement in the diagnostic performance of PI-RADS v2 with the addition of ADC value measurements (10). It is difficult to explain this discrepancy, which is likely multifactorial. Potential reasons include variability of ADC values across imaging platforms and protocols (11), differences in the ADC value threshold used in each study, and inter-reader variability of PI-RADS v2 (12), which would impact the sensitivity and

Table 4 - Upgrade of systematic biopsy – logistic regression analysis.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PI-RADS v2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.20</td>
<td>0.41</td>
<td>0.78</td>
</tr>
<tr>
<td>5</td>
<td>0.48</td>
<td>0.02</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>PSAD categories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.39</td>
<td>0.003</td>
<td>1.35</td>
</tr>
<tr>
<td>3</td>
<td>2.39</td>
<td>0.008</td>
<td>1.25</td>
</tr>
<tr>
<td>4</td>
<td>2.48</td>
<td>0.003</td>
<td>1.37</td>
</tr>
<tr>
<td>Number of lesions on MRI</td>
<td>1.41</td>
<td>0.02</td>
<td>1.06</td>
</tr>
<tr>
<td>Lesion diameter on MRI</td>
<td>0.76</td>
<td>0.06</td>
<td>0.57</td>
</tr>
</tbody>
</table>

**AUROC = 0.69 (95% CI = 0.64-0.73)**

**P** = probability; **CI** = confidence interval; **PI-RADS v2** = Prostate Imaging Reporting and Data System, version 2; **PSAD** = prostate-specific antigen density; **MRI** = magnetic resonance imaging; **AUROC** = area under the receiver-operating characteristic curve
specificity of the method, and therefore the incremental usefulness of ADC values. Yet, because at
any given institution these factors tend to be more or less constant, so does the range of ADC values
that are measured. Thus, although the range may differ across imaging sites, ADC values can be ea-
sily obtained and should better characterize disease status of patients imaged at individual centers.

PSAD has been previously shown to improve the diagnosis and characterization of lesions seen
on TRUS and mpMRI. Almost 30 years ago, Veneziano S. et al. showed that PSAD calculate using
TRUS could identify men who had an elevated PSA due to BPH rather than cancer (13). Later, Catalo-
na et al. showed that a PSAD \( \leq 0.15 \) could be used to predict favorable pathology on prostatectomy
(14). Similarly, PSAD can improve the accuracy of mpMRI; a PSAD \( \geq 0.15 \) doubles the rate of clinically
significant prostate cancer in men with PI-RADS v2 4 or 5 lesion (3). And Kotb et. al. suggest that
re-biopsy is not necessary in men prior negative biopsy, PSAD <0.15, and low PI-RADS score (15).

Our results show similar impact on the diagnosis of clinically significant prostate cancer. Although
the area under the ROC curve of PI-RADS v2 and PSAD was statistically larger than the area under
the ROC curve of PI-RADS v2 and ADC categorical, the difference between the two was not clinically
relevant. While either approach can be used, the interpretation and clinical application of a categorical
variable may be simpler and easier to understand.

PI-RADS v2 does not aim at identifying prostate cancer in areas without a visible lesion on
mpMRI. Yet, it is known that around 5 to 20% of clinically significant prostate cancers are identi-
fied in such areas (6, 7). In our population, upgrade on systematic biopsy was slightly more likely
to be seen in men with PSAD \( \geq 0.15 \) and multiple small PI-RADS v2 3 or 4 lesions on MRI. The
presence of a PI-RADS v2 5 lesion, though, made upgrade less likely, as these often already repre-
sent clinically significant prostate cancer. As size is one of the criteria to assign a PI-RADS v2 score
5 to a lesion, it is not surprising that small lesions are more likely than large ones to be associated
with upgrade on systematic biopsy. It is impor-
tant to note that multifocal clinically significant prostate cancer is not excluded by the presence
of a PI-RADS v2 5 lesion. And multifocality may explain the association of multiple lesions on MRI
and upgrade on systematic biopsy.

The PI-RADS guidelines asks for the sole assessment of imaging findings, but basic clinical
data, e.g. total serum PSA, is routinely available to radiologists at the time of imaging interpretation.
This data is utilized daily by urologists to assist

Figure 3 - Prediction of upgrade on systematic biopsy, ROC curve. The area under the ROC curve of the model was 0.69, only marginally discriminating between men in whom systematic biopsy will and will not lead to upgrade to clinically significant prostate cancer.

![ROC curve](image_url)
with management decisions. Similarly, radiologists should not ignore other existing information, but incorporate these to practice to better serve our patients and colleagues. PI-RADS is a work in progress and, as new data becomes available, revised versions are expected to be released. Until large studies that investigate the impact of imaging on hard outcomes as death or metastases become available, the identification of clinically significant prostate cancer will continue to serve a surrogate marker. It is our hope that the results of this study help to develop a new version of PI-RADS, enhance the characterization of lesions visible on mpMRI, and improve the identification of men with clinically significant prostate cancer.

This study has limitations inherent to a retrospective, single institution research. The rate of clinically significant prostate cancer per PI-RADS v2 scores was lower than the average in the literature (16), suggesting a high sensitivity threshold of readers. This may reflect different experience of the various readers who interpreted the scans. Accordingly, the impact of ADC and PSAD of PI-RADS v2 may not be the same at other sites with different sensitivity and specificity profiles. This study was based on the review of medical charts, so images nor slides were re-analyzed. We made this option because we aimed at learning the value of using ADC and PSAD in daily practice, but the method is prone to errors in data collection. To minimize this problem, the authors who collected the data were trained, we used a standardized abstraction forms, and we had a quality and assurance process in place. Our standard of reference was not prostatectomy, but TRUS-MRI fusion biopsy, and therefore only samples of the gland were considered to determine our outcomes. We made this option because TRUS-MRI fusion biopsy is quickly becoming the standard of practice and to avoid selecting only men who underwent surgery, which would have inflated our sample with patients diagnosed with clinically significant prostate cancer.

CONCLUSIONS

ADC values and PSAD help to characterize lesions that are assigned a PI-RADS v2 score 4 or 5 as clinically significant prostate cancer. The predictive value of categorized ADC values and PSAD are not markedly different from the continuous versions and can, therefore, be utilized in daily practice. Men with PSAD ≥0.15 and multiple small lesions assigned a PI-RADS v2 score 3 or 4 are marginally more likely to be upgraded on systematic biopsy.

CONFLICT OF INTEREST

None declared.

REFERENCES


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San Francisco, CA, 95143, USA
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E-mail: antonio.westphalen@ucsf.edu
Is possible to rule out clinically significant prostate cancer using PI-RADS v2 for the assessment of prostate MRI?

Publio Cesar Cavalcanti Viana 1, Natally Horvat 1, Valter Ribeiro dos Santos Júnior 1, Thais Carneiro Lima 1, Davi dos Santos Romão 1, Luciana Mendes de Oliveira Cerri 1, Marília Germanos de Castro 2, Herbert Alberto Vargas 3, Júlia Azevedo Miranda 1, Claudia da Costa Leite 1, Giovanni Guido Cerri 1

1 Departamento de Radiologia do Hospital Sírio-Libanês, São Paulo, SP, Brasil; 2 Departamento de Patologia do Hospital Sírio-Libanês, São Paulo, SP, Brasil; 3 Departamento de Radiologia, Memorial Sloan Kettering Cancer Center, Nova York, NY, EUA

ABSTRACT

Objectives: To evaluate the diagnostic performance and interobserver agreement of PI-RADS v2.

Materials and Methods: In this Institutional Review Board approved single-center retrospective study, 98 patients with clinically suspected PCa who underwent 3-T multiparametric MRI followed by MRI/TRUS fusion-guided prostate biopsy were included from June 2013 to February 2015. Two radiologists (R1 and R2) with 8 and 1 years of experience in abdominal radiology reviewed the MRI scans and assigned PI-RADS v2 scores in all prostate zones. PI-RADS v2 were compared to MRI/TRUS fusion-guided biopsy results, which were classified as negative, PCa, and significant PCa (sPCa).

Results: Sensitivity, specificity, NPV, PPV and accuracy for PCa was 85.7% (same for all metrics) for R1 and 81.6%, 79.6%, 81.2%, 80.0% and 80.6% for R2. For detecting sPCa, the corresponding values were 95.3%, 85.4%, 95.9%, 81.7% and 89.8% for R1 and 93.0%, 81.8%, 93.7%, 86.7% and 86.7% for R2. There was substantial interobserver agreement in assigning PI-RADS v2 score as negative (1, 2, 3) or positive (4, 5) (Kappa=0.78). On multivariate analysis, PI-RADS v2 (p <0.001) was the only independent predictor of sPCa compared with age, abnormal DRE, prostate volume, PSA and PSA density.

Conclusions: Our study population demonstrated that PI-RADS v2 had high diagnostic accuracy, substantial interobserver agreement, and it was the only independent predictor of sPCa.

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancer, being the most commonly diagnosed cancer in men in the United States and the second most common one worldwide (1). The detection of clinically significant PCa (sPCa) is gathering growing interest in the literature, because a significant number of patients with indolent tumor has been unnecessarily treated with aggressive treatment, with potential complications (2).

International PCa diagnosis and management guidelines are predominantly based on literature originating from developed countries (3-6).
This is also the case for cancer imaging guidelines, such as the Prostate Imaging Reporting and Data System (PI-RADS) (7). The use of multiparametric prostate magnetic resonance imaging (mpMRI) has increased exponentially in the last few years in several countries, supported by vast literature demonstrating its usefulness in multiple contexts regarding PCA diagnosis, treatment planning and selection, determination of active surveillance eligibility and follow-up and post-treatment assessment. PI-RADS was originally introduced in 2012 (8) and updated as a version 2.0 in 2015 (7), with the primary aim of standardizing multiparametric prostate MRI acquisition and reporting. It is based on a combination of the existing literature synthesized by an expert panel.

There is increasing literature validating the use of PI-RADS v2 concerning accuracy and repeatability (9-13). In this scenario, the purpose of the study was to evaluate the diagnostic performance and interobserver agreement of PI-RADS v2 in detecting clinically significant PCa in a Brazilian population.

MATERIALS AND METHODS

Study population

In this single-center retrospective study, Institutional Review Board approval was obtained and the requirement for informed written consent was waived. The Hospital Sírio-Libanês database was retrospectively queried to identify patients who underwent 3-T mpMRI followed by MRI/TRUS fusion-guided prostate biopsy from June 2013 to February 2015.

Inclusion criteria were: (a) patients with clinically suspected PCa, based on increased PSA levels and/or abnormal digital rectal examination, and (b) MRI/TRUS fusion-guided prostate biopsy performed within 6 weeks following the date of the 3-T mpMRI. The exclusion criteria were patients with previous diagnosis of PCa, history of prostate biopsy up to 3 months before the MRI, or histological data unavailable for review.

We included 106 consecutive patients who underwent 3-T mpMRI followed by MRI/TRUS fusion-guided prostate biopsy within 6 weeks during the selected period. We excluded 8 patients: 5 patients with known PCa, 2 patients with recent prostate biopsy, and 1 patient due to absence of histological samples. All 98 remaining patients were included in the final study population. The median interval between the 3-T mpMRI and MRI/TRUS fusion-guided prostate biopsy was 14 days (range, 2-42).

Prostate mpMRI

Prostate mpMRI was performed using a 3.0-T GE Signa HDxt MR Scanner (GE Healthcare, Milwaukee, USA) with receive only pelvic phased-array coil with 18 channels without endorectal coil. All patients fasted for at least 4 hours before the examination. The prostate images were acquired before and after intravenous injection of 0.2mL/kg of gadoversetamide (Opti-mark; Mallinckrodt Inc., St. Louis, MO) at a rate of 3mL/second by power injector, followed by 20mL of saline flush.

The MRI examinations were performed using a standardized clinical protocol as recommended in PI-RADS v2 (7), including T2-weighted imaging (T2WI), dynamic contrast-enhanced (DCE) imaging, and diffusion-weighted imaging (DWI) (Table-1).

Image analysis

The radiologists were blinded to clinical status, initial report, laboratory tests and histopathological results.

Both readers had been routinely using PI-RADS v2 as part of their clinical practice prior to this study. In addition, both readers met for one hour and reviewed the PI-RADS v2 literature and instructions together with 15mpMRI cases (not in the study population) to practice and align interpretation of the scoring system (7). In patients with more than 1 lesion, the index lesion (IL) was selected. We defined as IL the one with the highest PI-RADS score, when multiple lesions had the same score, the largest one, measured as the largest dimension on T2-weighted images in any plane. The ILs were described by location, dimensions (mm), and PI-RADS v2 score. Prostate mpMRI exams were considered positive if the PI-RADS scores were 4 or 5.
Transrectal US-guided biopsy

All patients underwent MRI/TRUS fusion-guided prostate biopsy using an iU22 Ultrasound System (Philips, Amsterdam, Netherlands), with an operating bandwidth of 8-4MHz equipped with an end-fire endorectal biopsy probe. All biopsies were performed by a board-certificated interventional radiologist X.Z. with 20 years of experience and were supervised by the radiologist who had performed the prostate mpMRI during clinical routine. Standardized 12-core biopsy was performed and additional cores were taken from the suspicious areas in mpMRI using the image fusion approach. In this method, transrectal TRUS was performed by the radiologist and the MRI, which was performed previously, was fused with the real-time TRUS using a digital overlap. Therefore, the suspicious areas previously delineated on MRI were possible to be target on US. All prostatic cores were obtained by using an 18-gauge biopsy needle (Argon Medical Devices, Athens, Texas, USA) and were labeled to identify the location. The median number of biopsy cores per patient was 21 (IQR, 18–22). Of these, 12 standardized core biopsies and 6 to 10 were made by the MRI/TRUS fusion technique directed to the suspicious areas.

Pathological analysis

Two genitourinary pathologists (X.X.Y and Y.Y.H.) with 20 and 10 years of experience reviewed the samples according to International Society of Urological Pathology Consensus (14), regarding the presence of tumor, if present, the Gleason score, the number of cores with tumor and the percentage of tumor in each core.

Statistical analysis

We classified the PI-RADS v2 as negative (scores 1 to 3) or positive (scores 4 or 5) and final diagnosis, based on clinical status and biopsy results, as negative, any PCa, and significant sPCa (sPCa). sPCa was defined as those of non-very low risk group, according to risk classification adopted on National Comprehensive Cancer Network Guidelines (NCCN), including low, intermediate, high, and very high risk, and metastatic (3). Men with all of the following tumor characteristics are categorized in the very-low-risk group: clinical stage T1c, biopsy Gleason score ≤6/Grade Group-1, PSA <10ng/mL, presence of disease in fewer than 3 biopsy cores, ≤50% prostate cancer involvement in any core, and PSA density <0.15ng/mL/g. Data were analyzed through the statistical program Software SPSS 22.0 version, using chi-square
and Mann-Whitney U tests. Multivariate logistic regression was also used if association were detected on univariate analysis. P values p <0.05 were considered significant. Interobserver agreement on PI-RADS v2 (grouped as scores 1-3 vs. 4-5) was assessed using weighted Kappa. Kappa values were interpreted as follows: 0.00-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, almost perfect agreement (15).

RESULTS

Baseline demographics and prostate mpMRI findings

Considering the skewed distribution of our data we used median and IQR to demonstrate our results. There were 98 patients with a median age of 60 years (IQR: 54-69), median serum PSA of 6.3 ng/mL (IQR: 4.5-9.7), median PSA density of 0.15ng/mL/g (IQR: 0.09-0.23) and median prostate volume of 32cm³ (IQR: 40.5-56.8). Twenty-one of the 98 patients (21.4%) had an abnormal digital rectal examination.

The mean size of the index lesion on mpMRI was 14.4mm (R1=14.3mm; R2=14.5mm). According to R1 and R2, 49/98 (50%) and 50/98 (51%) of patients were assigned PI-RADS scores of 4 or 5. Forty-nine of 98 (50%) men were diagnosed with PCa and 43/98 (44%) with sPCa, 84% were located in the peripheral zone and 16% in the transition zone, for both PCa and sPCa combined. Among the 49 patients with PCa, 11 (22%) were assigned a Gleason score of 6 and 38 (78%) the Gleason scores were greater than or equal to 7 (median, 7; IQR: 7-8). The characteristics of the patients without PCa, with PCa and sPCa are displayed in Table-2. The distribution of Gleason score (6, 7, 8, 9 and 10) in groups for patients with sPCa is displayed in Table-3. The characteristics of the patients with sPCa are displayed in Table-2. The distribution of Gleason score (6, 7, 8, 9 and 10) in groups is displayed in Table-3, the distribution of PI-RADS classification in each category is displayed in Table-4, the accuracies, sensitivities, specificities, negative predictive values, and positive predictive values of PI-RADS v2 for the diagnosis of PCa and sPCa are displayed in Table-5 and the numbers that allow estimation of the different diagnostic accuracy parameters are displayed in Table-5.1.

Diagnostic performance of prostate mpMRI

For the detection of PCa, R1 had the same sensitivity, specificity, NPV, PPV and accuracy (85.7%). The sensitivity and specificity of R1 for the detection of sPCa were 95.3% and 85.4%, and the NPV and PPV were 95.9% and 83.7%, respectively. The overall accuracy for detection of sPCa was 89.8%.

For R2, the sensitivity, specificity, NPN and PPV for detection of PCa were 81.6%, 79.6%, 81.2%, and 80.0%, respectively and the accuracy was 80.6%. Considering the sPCa, the sensitivity and specificity were 93.0% and 81.8%, the NPV and PPV were 93.7% and 86.7% and the accuracy was 86.7%. The performances of readers separately are summarized in Table-3.

The interobserver agreement in assigning PI-RADS v2 score was substantial (Kappa=0.78).

sPCa missed on prostate mpMRI

R1 missed 2 patients with sPCa, one with PSA density >0.15ng/mL/g and one with Gleason of 8 (4+4). R2 missed the same 2 cases in addition...
Table 4 - Distribution of PIRADS classification in each category.

<table>
<thead>
<tr>
<th>WITHOUT PCa</th>
<th>TOTAL CANCER</th>
<th>sPCa</th>
<th>PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAD 1</td>
<td>RAD 2</td>
<td>RAD 1</td>
</tr>
<tr>
<td>PI-RADS 1 or 2</td>
<td>28/49 (57.1%)</td>
<td>32/49 (65.3%)</td>
<td>3/49 (6.1%)</td>
</tr>
<tr>
<td>PI-RADS 3</td>
<td>13/49 (26.5%)</td>
<td>7/49 (14.2%)</td>
<td>4/49 (8.1%)</td>
</tr>
<tr>
<td>PI-RADS 4</td>
<td>5/49 (10.2%)</td>
<td>10/49 (20.4%)</td>
<td>23/49 (46.9%)</td>
</tr>
<tr>
<td>PI-RADS 5</td>
<td>2/49 (4%)</td>
<td>0/49 (0%)</td>
<td>19/49 (38.7%)</td>
</tr>
</tbody>
</table>

Table 5 - Accuracies, sensitivities, specificities, negative predictive values, and positive predictive values of PI-RADSv2 for the diagnosis of PCa and sPCa.

<table>
<thead>
<tr>
<th>WITHOUT PCa</th>
<th>TOTAL CANCER</th>
<th>sPCa</th>
<th>PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAD 1</td>
<td>RAD 2</td>
<td>RAD 1</td>
</tr>
<tr>
<td>PI-RADS 1, 2 or 3</td>
<td>42/49 (85.7%)</td>
<td>39/49 (79.6%)</td>
<td>7/49 (14.3%)</td>
</tr>
<tr>
<td>PI-RADS 4 or 5</td>
<td>7/49 (14.3%)</td>
<td>10/49 (20.4%)</td>
<td>42/49 (85.7%)</td>
</tr>
</tbody>
</table>

Table 5.1 - Numbers that allow estimation of the different diagnostic accuracy parameters.

<table>
<thead>
<tr>
<th>PIRADS (RAD 1)</th>
<th>Patients with sPCa</th>
<th>Patients without sPCa</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (4 or 5)</td>
<td>41 (95.3%)</td>
<td>8 (14.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative (1, 2 or 3)</td>
<td>2 (4.7%)</td>
<td>47 (85.5%)</td>
<td></td>
</tr>
<tr>
<td>PIRADS (RAD 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (4 or 5)</td>
<td>40 (93.0%)</td>
<td>10 (18.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative (1, 2 or 3)</td>
<td>3 (7.0%)</td>
<td>45 (81.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 - Distribution of PIRADS classification in each category.

<table>
<thead>
<tr>
<th>WITHOUT PCa</th>
<th>TOTAL CANCER</th>
<th>sPCa</th>
<th>PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAD 1</td>
<td>RAD 2</td>
<td>RAD 1</td>
</tr>
<tr>
<td>PI-RADS 1, 2 or 3</td>
<td>42/49 (85.7%)</td>
<td>39/49 (79.6%)</td>
<td>7/49 (14.3%)</td>
</tr>
<tr>
<td>PI-RADS 4 or 5</td>
<td>7/49 (14.3%)</td>
<td>10/49 (20.4%)</td>
<td>42/49 (85.7%)</td>
</tr>
</tbody>
</table>

Table 5.1 - Numbers that allow estimation of the different diagnostic accuracy parameters.

<table>
<thead>
<tr>
<th>PIRADS (RAD 1)</th>
<th>Patients with PCa</th>
<th>Patients without PCa</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (4 or 5)</td>
<td>42 (85.7%)</td>
<td>7 (14.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative (1, 2 or 3)</td>
<td>7 (14.3%)</td>
<td>42 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>PIRADS (RAD 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (4 or 5)</td>
<td>40 (8.6%)</td>
<td>10 (20.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative (1, 2 or 3)</td>
<td>9 (18.4%)</td>
<td>39 (79.6%)</td>
<td></td>
</tr>
</tbody>
</table>
to another case with serum PSA of 10ng/mL and more than 3 prostate biopsy cores positive and 90% cancer in any core. All sPCa missed were located in the peripheral zone. Figure-1 illustrates one representative false negative case. Figure-2 demonstrates a case of disagreement between the readers.

Clinical risk stratification

Serum PSA, PSA density, prostate volume and PI-RADS v2 scores were associated with sPCa on univariate analysis (p <0.05 in each). However, on multivariate analysis, PI-RADS v2 was the only significant independent predictor of sPCa with an odds ratio of 120 (95% CI: 24-599, p <0.001) for R1 and odds ratio of 60 (95% CI: 15-233, p <0.001) for R2.

Figure 1 - A focal lesion was identified by both radiologists on T2WI (a) in the prostate left middle third, but with slightly restricted diffusion (c, d) and negative perfusion (b). PI-RADS final score 3 was assigned by the two readers. Pathological analysis revealed Gleason 8 in the right middle third and Gleason 7 in the left.

Figure 2 - MpMRI showing suspected lesion on T1WI (a), T2WI (b), DWI (c), ADC map (d) and perfusion (e) sequences. The radiologist 1 identified lesion in the prostate right middle third and assigned as PI-RADS 5 with extra-prostatic extension. The same lesion was scored as 2 for the radiologist 2. The pathological analysis diagnosed a Gleason 6 in the right middle third. The patient was classified as having significant cancer due to PSA of 10ng/mL. In this case, the presence of blood may have limited the interpretation of the reader 2.

DISCUSSION

In our study cohort of 98 Brazilian patients with clinically suspected PCa, we found accuracy for both readers in detecting sPCa on mpMRI using PI-RADS v2 higher than 86% and a NPV higher than 93%. Our study also demonstrates a substantial interobserver agreement in assessing the PI-RADS v2 score as negative or positive. Furthermore, PI-RADS v2 was the only independent predictor of sPCa on multivariate analysis.

Using PI-RADS v2 it was possible to rule out the vast majority of sPCa with substantial reproducibility between 2 independent radiologists, even broadening the criteria of significant tumors as we did including low risk patients as sPCa (3). The reason that motivated us to include it was the fact that our gold standard was transrectal biopsy, and it is known that there is a potential risk of patients classified as low risk PCa on biopsy to end up with sPCa after radical prostatectomy (16, 17). On the other hand, in contrast to other studies, on multivariate analysis PSA density was not significantly correlated with sPCa, probably due to our small sample size.
With regards to accuracy of PI-RADS v2, our results are consistent with prior studies, which have reported accuracies ranging from 70% to 87% (9, 18). Our results are equivalent even if we compare it with studies in which the endorectal coil was used (9). These reinforce the notion that 3T mpMRI with pelvic phased-array coil is comparable to 1.5TmpMRI for detection of PCa (19).

The interobserver agreement in assigning the PI-RADS v2 varies in the literature from moderate to substantial (9-11, 18), being the moderate more frequent, even when selected key-images were used in these studies. Our substantial interobserver agreement (kappa=0.78) is comparable with that demonstrated by Kasel-Seibert et al. (kappa=0.68) (10), which also evaluated the interobserver agreement between radiologists from the same institution. Nevertheless, it was better than the results demonstrated by Muller et al. (kappa=0.46) (9) and Rosenkrantz et al. (kappa=0.59 in peripheral zone; and kappa=0.51 in transition zone) (11) among readers from different centers.

In the other study from Brazil, 54 patients were also retrospectively included and 2 readers with different levels of experience in uroradiology (1 and 10 years) reviewed the mpMRI. The primary outcome was the histological analysis after biopsy or surgery, but without classification between PCa and sPCa. In comparison to this study, our results of diagnostic performance of mpMRI in the diagnosis of PCa were overall similar; however, our values of NPV were higher (81%-86% vs. 66%-67%) whereas our PPV results were slightly lower (80% to 86% vs. 87% to 89%). With regards to interobserver agreement, our result was better than those presented by them (kappa=0.78 vs. kappa=0.53), but it was not specified if the analysis was made considering each score separately or grouped in negative vs positive (18).

Our observations suggest that PI-RADS v2 is feasible to be implemented in institutions without previous experience on that, and it is reproducible between readers with different expertise after a specific training. Our results are similar with those performed in different study populations such as in the US and Europe, which emphasize the added value of PI-RADS v2 to standardize the acquisition, interpretation, and reporting of prostate mpMRI. Using PI-RADS v2 it was possible to rule out the vast majority of sPCa, however, the fact that the readers did not detect some patients with sPCa reinforces that the approach of PCa should not be focus on a sole exam, but on a multidisciplinary approach, which includes the mpMRI.

There are several limitations to our study. First, it was a retrospective assessment with inherent limitations of this study design and small sample size. In addition, the gold standard was transrectal MR/ultrasound fusion biopsy, which is known to potentially underestimate the diagnosis and grade of the PCa, on the other hand it reflects the reality of the clinical management of patients with suspected PCa, who don’t all proceed to surgery which provides the best standard of reference (whole-mount prostatectomy specimen). Considering that, our results may be overestimated. Furthermore, considering that we did not use whole-mount as the reference standard it was not possible to do a precise correlation between mpMRI and pathology. Additionally, even though the readers have different levels of expertise, they work at the same institution which could have overestimated the inter-observer agreement; however, they had different educational background. Finally, considering that the study was performed at a comprehensive cancer hospital, we may have included a high proportion of significant PCa when compared with other center, it also could have overestimate the performance of the PI-RADS and of the readers.

In conclusion, our study in a Brazilian population demonstrates high diagnostic accuracy of PI-RADS, and also a substantial interobserver agreement in differentiating PI-RADS v2 1, 2 and 3 from PI-RADS 4 and 5 between readers with different levels of expertise. Overall, the mpMRI using PI-RADS v2 could rule out the vast majority of sPCa and it was the only independent predictor of sPCa.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

None declared.

REFERENCES


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A census of laparoscopic and robotic urological practice: a survey of minimally invasive surgery department of the Brazilian Society of Urology

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1 Hospital Monte Klinikum, Fortaleza, CE, Brasil; 2 Hospital Albert Einstein, São Paulo, SP, Brasil; 3 Hospital Marcelino Champagnat, Curitiba, PR, Brasil; 4 Hospital Federal dos Servidores do Estado, Rio de Janeiro, RJ, Brasil

ABSTRACT

Minimally invasive urologic surgery has been developing in Brazil and now is a routine part of care in many regions and patients with different conditions benefit from it. Training in laparoscopic and robotic surgery has evolved and concerns exist both over the quality of surgical training and the practical effect on results of the urological training. This is an unprecedented study which undertook a census to determine the current state of laparoscopic and robotic urological practice and to know the main barriers to adequate practice in Brazil. In August 2017, surveys, consisting of an anonymous questionnaire with 15 questions, were sent via internet to the mailing list of the Brazilian Society of Urology (SBU). With these data, activities related to laparoscopy and robotic surgery of our urologists and the main difficulties and barriers to practice laparoscopy and robotic surgery were evaluated. In our survey, 413 questionnaires were completed. Majority of the responders were currently working in the southeast region of Brazil (52.1%) and 75.5% of the surgeons performed laparoscopic surgery while, only 12.8%, robotic surgery. The lack of experience on the technique and the lack of equipment were the main barriers and difficulties for not executing laparoscopic and robotic surgeries, respectively. Proper longitudinal training and access to good equipment in minimally invasive surgery are still barriers for urologists in our country.

INTRODUCTION

Urological laparoscopic surgery has been steadily developing and is now a part of the routine care of many urological conditions. However, laparoscopic surgery poses specific challenges that require acquisition of difficult skills and lead to a steeper learning curve when compared with open surgery (1). Training in laparoscopic surgery has evolved since its inception in the 1980s with the creation of multiple simulation centers where surgeons can acquire skills outside of the operating room (2, 3).

Since the introduction of robotic surgical systems at the last century, the growth of robotic surgical practice in urology has been exponential (4). This growth, in the use of robotic platforms, has occurred without a simultaneous shift in the
manner by which training takes place (5). Concerns exist both over the quality of robotic surgical training and the effect of robotic practice has had on urological training in general (6).

The objectives of this study are to undertake a census to determine the current state of laparoscopic and robotic urological practice and to know the main barriers to adequate practice in Brazil.

MATERIALS AND METHODS

In August 2017, the department of minimally invasive surgery of the Brazilian Society of Urology (SBU) designed non-validated surveys based on the vast experience of the members of the department, consisting of an anonymous questionnaire with 15 questions prepared through the Google® Forms website (7). This method of questions was sent via internet through the mailing list of the SBU to all active members and a link to the survey website was set in the covering letter. Responses were taken using the automated process of the website and were kept open for 3 months.

A minimum sample was calculated so that the data could be significantly analyzed. The calculation was used for sampling a finite population, adopting the error of 5% and confidence interval of 95%, reaching the result of a minimum sample of 359 participants (8).

The main topics evaluated in the survey were if the urologist performed minimally invasive surgery, how many they operated in average, which exact surgery they performed by pure laparoscopy or robotic, motive for not performing minimally invasive surgery, how long they were in the field, demographic information and if they would participate in hands-on courses. In some questions, participants were able to choose more than one response (Table-1).

With these data, activities related to laparoscopy and robotic surgery of our urologists and the main difficulties and barriers to minimally invasive practice were evaluated and we correlated the experience as urologist, the region in Brazil they worked and the area they were located with performing video surgery and robotic surgery using the Chi-square Test of independence.

All the answers were collected in the Google® Forms’ database in the internet and the information was transferred to Microsoft® Excel. Subsequently, analysis was done using IBM SPSS Statistics for Windows, Version 22.0 (IBM, New York, USA). A p <0.05 was considered to indicate statistical significance.

RESULTS

In all, 413 questionnaires were completed, sent and analyzed. The majority of the respondents were currently working in the Southeast region of Brazil (52.1%), followed by South region (20.3%), Northeast region (17.9%), Mid-west region (6.5%) and North region (3.1%). Urologists currently working in the capital corresponded to 55.7%, while 44.3% of the respondents were in the interior.

Considering an estimated total number of urologists with a specialist title in Brazil to be 5328 (9) and the 413 questionnaires analyzed, the overall urology specialist’s response rate was 7.75% and the 95% confidence interval (CI) was 7.03%-8.47%.

Among the respondents, 61.9% were working in cities with >500,000 inhabitants, 28.9% in cities with 100-500,000 inhabitants and 9.2% in cities with <100,000 inhabitants.

Most part of respondents had less than 10 years as urologists (50.9%) and experienced urologists were less common (23.2% between 10 to 20 years and 25.9% with more than 20 years).

In our survey, 75.5% of the surgeons performed laparoscopic surgery and only 12.8% robotic surgery. When asked about the number of laparoscopic surgeries performed per month, 61.8% were performing five procedures, 24.9% between five to ten surgeries and 13.2% more than 10 procedures. Among robotic surgeons, the number of monthly surgeries were 5 or less in 77.4%, between 5 to 10 in 14.5% and more than 10 in 8.1%.

Including the laparoscopic procedures, the most frequently done is total or radical nephrectomy by 95.7% of respondents, followed by pyeloplasty (85.2%). Partial nephrectomy and adrenalectomy are performed by 72.5% of laparoscopic urologists. Less than half of laparoscopic urologists made radical prostatectomies (47.2%), sacrocolpopexy
Table 1 - Questions and possible answers sent for SBU members.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Possible answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you perform videosurgery?</td>
<td>Yes or No.</td>
</tr>
<tr>
<td>If yes, how many videosurgeries do you perform in a month? (average)</td>
<td>0-5 or 5-10 or &gt;10</td>
</tr>
<tr>
<td>If laparoscopy is performed, which of the following do you do?*</td>
<td>Total and radical nephrectomy, Partial nephrectomy, Radical prostatectomy, Prostatectomy for benign prostatic hyperplasia (BPH), Cystectomy, Pyeloplasty, Sacrocolpopexy, Adrenalectomy, Others</td>
</tr>
<tr>
<td>If you answered no or consider doing a small number of procedures, what would be the reason?*</td>
<td>Lack of trained support staff (assistants, nursing, etc.), Lack of patients, Lack of practical experience in the method, Lack of equipment/infrastructure in the hospital I attend, Lack of theoretical knowledge about the method</td>
</tr>
<tr>
<td>Do you perform robotic surgery?</td>
<td>Yes or No.</td>
</tr>
<tr>
<td>If yes, how many robotic surgeries do you perform in a month? (average)</td>
<td>0-5 or 5-10 or &gt;10</td>
</tr>
<tr>
<td>If robotic surgery is performed, which of the following do you do?*</td>
<td>Total and radical nephrectomy, Partial nephrectomy, Radical prostatectomy, Prostatectomy for BPH, Cystectomy, Pyeloplasty, Sacrocolpopexy, Adrenalectomy, Others</td>
</tr>
<tr>
<td>If you answered no or consider doing a small number of robotic procedures, what would be the reason?*</td>
<td>Lack of trained support staff (assistants, nursing, etc.), Lack of patients, Lack of practical experience in the method, Lack of equipment/infrastructure in the hospital I attend, Lack of theoretical knowledge about the method</td>
</tr>
<tr>
<td>How long have you been a professional urologist? (Years)</td>
<td>0-10 or 10-20 or &gt;20</td>
</tr>
<tr>
<td>What region of Brazil do you perform your urological activity?</td>
<td>Northeast or Southeast or Mid-West or South or North.</td>
</tr>
<tr>
<td>Your area of activity is located in the interior or capital of the state?</td>
<td>Interior or Capital</td>
</tr>
<tr>
<td>What is the approximate number of inhabitants of the municipality in which you operate? (Thousands)</td>
<td>&lt;100 or 100-500 or &gt;500</td>
</tr>
<tr>
<td>Would you participate in theoretical and practical courses (hands-on and live surgeries) taught by national and international experts in your region?</td>
<td>Yes or No.</td>
</tr>
<tr>
<td>How far would you travel to participate in this type of course? (Km)</td>
<td>0-50 or 50-200 or &gt;200</td>
</tr>
<tr>
<td>Give a suggestion of a city of your region to carry out a course of this type</td>
<td>Open question</td>
</tr>
</tbody>
</table>

*Participants were able to choose more than one response.
(18.4%), prostatectomy for BPH (17.2%) or radical cystectomy (12.1%) (Figure-1).

All robotic surgeons inquired performed radical prostatectomy (100%) and 86.8%, partial nephrectomy. Also, urologists trained in robotic surgery responded that they performed total or radical nephrectomy (56.6%), pyeloplasty (50.9%), adrenalectomy (34%), prostatectomy for BPH (34%), sacrocolpopexy (20.8%) or, less commonly, radical cystectomy (18.9%) (Figure-2).

When inquired about the main difficulties for not executing or performing a small number of laparoscopic surgeries, the lack of practical experience on the method was pointed out in 62.8% of responders. Following, the lack of patients (39.2%), of equipment and structure (25.6%), of trained support staff (14.4%) and of theoretical knowledge (9.6%) were highlighted (Figure-3).

Mains barriers and difficulties for not executing robotic surgery were the lack of equipment/infrastructure (74.6%), of experience in this modality (62.2%), of theoretical knowledge (30.7%), of trained support staff (24.5%) and lack of patients (23.9%) (Figure-4).
Among all respondents, 78% would participate in theoretical and practical courses (hands-on and live surgeries) taught by national and international experts.

A Chi-square test of independence was calculated comparing the time as they worked as urologists and if they performed laparoscopy which found a significant interaction ($\chi^2(2)=20.576$, $p<0.05$) and if they performed robotic surgery which was not significant ($p=0.507$).

A Chi-square test of independence was calculated comparing the region in our country they worked and if they performed laparoscopy which did not found a significant interaction ($\chi^2(4)=5.870$, $p=0.209$) and if they performed robotic surgery which was significant ($\chi^2(4)=11.745$, $p=0.019$).

A Chi-square test of independence was calculated comparing the area (capital or interior) they worked and if they performed laparoscopy which found a significant interaction ($\chi^2(2)=34.749$, $p<0.05$) and if they performed robotic surgery which was significant ($\chi^2(2)=27.200$, $p<0.05$).

**DISCUSSION**

This study, for the first time, provides an overview of laparoscopic and robotic urological practice in Brazil. In our country, the first laparos-
copic surgery was done in 1991 in Rio de Janeiro and the initial experience in robotic surgery took place at São Paulo in 2008 (9).

A significant number of responses were obtained and the distribution of the answers were very similar of that of the urologists of our country according to our Federal Medical Council (10). All 5328 Brazilian urologists are divided as follows: North region (4.3%), Northeast region (16.5%), Southeast region (52.2%), South (16.9%) and Mid-west region (10%) (10). While our responses were obtained from the following regions: North region (3.1%), Northeast region (17.9%), Southeast region (52.1%), South (20.3%) and Mid-west region (6.5%).

Our study has some limitations. Since it was an internet survey, a bias was introduced to those who regularly check and use e-mail. Urologists, who respond to e-mail surveys, may be more likely to embrace technological advances and answer questions involving new and minimally invasive techniques. Also, the survey was sent only to those who are members of the SBU.

Half of the urologists who participated of the census (50.2%) had less than 10 years of experience, 23.2% had a professional career between 10 to 20 years and 25.9% had more than 20 years. The median time of experience of all 5328 urologists in Brazil is 23.4 years according to our federal council (10).

Considering that laparoscopy was introduced more frequently in our resident’s practice in the 2000s, the years of experience as formed urologists might also have a significant consequence about questions of laparoscopic surgery, once urologists are more likely to perform laparoscopic procedures if they were trained during residency than if they had no experience (11, 12). The percentage of those who perform laparoscopic surgery is 75.5%, which demonstrates a strong implementation of this technique among the urologists of our country. Among these professionals, 56.4% have less than 10 years of experience, 22.7% have between 10 to 20 years and 20.8% have more than 20 years as specialists (p <0.05).

As robotic surgery was initiated relatively 10 years ago in Brazil, the training occurred outside public hospitals with residents, and more experienced urologists in private’s hospitals were able to train with the robotic platform (9). In our survey, between those who performed robotic surgery, 43.3% had less than 10 years of experience, 26.4% between 10 to 20 years and 30.1% more than 20 years. We demonstrate that the majority (56.5%) of robotic surgeons inquired in Brazil have more than 10 years as specialists (p=0.507).

Total or radical nephrectomy is the most performed procedure by urologic laparoscopists (95.7%) and partial nephrectomy which had an increasing number of indications, is less commonly performed (72.5%) probably due to major complexity in some cases. Total or radical robotic-assisted nephrectomy is performed only by 56.6% of the surgeons already trained and could be explained due to lesser complexity, high costs and similar oncological and functional results when compared to pure laparoscopic technique. Nevertheless, partial nephrectomy, which is theoretically more complex and has advantages with the robotic platform, is performed by 86.8% of robotic surgeons.

Perhaps, the more complex steps in pure laparoscopic radical prostatectomy might be the main cause of only 47.2% being able to perform this technique and, on the other hand, 100% of robotic surgeons perform the robotic radical prostatectomy (13).

The main limitation in performing laparoscopic procedures is, the lack of practical experience with the technique (62.8%). Other factors considered relevant were the lack of patients (39.2%) and of equipment and structure (25.6%). In Brazil, we have several difficulties in our public health system, like lack of equipment for minimally invasive surgery, infrastructure and trained teams, not only in the interior of the country but also in some less developed capitals.

On the other hand, when we observe robotics surgeries, the main barriers are availability and access to the robotic platform (74.6%), followed by the lack of experience (62.2%). The small number of robotic platforms, around 30, when the census was distributed between August and October of 2017 and the limitations imposed, by the hospitals, to practice, explain these related difficulties. Almost all robots in Brazil are situated at the capitals, except for one, in
the interior of São Paulo, which reflects a bigger proportion of robotic surgeries performed in the capitals of the states of Brazil.

CONCLUSIONS

At our country, we have specific difficulties on the development of minimally invasive technologies, mainly in some regions, including the lack of equipment, experience and trained support staff. There are still barriers like high costs of the robotic platform, few urologists able to practice on the robotic platform and inadequate medical compensation (some minimally invasive surgeries are not included in the medical insurance fee hall).

CONFLICT OF INTEREST

None declared.

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Intraoperative serious complications of laparoscopic urological surgeries: a single institute experience of 4,380 procedures

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ABSTRACT

This study aimed to share a single institute experience of 4,380 procedures about intraoperative serious complications of laparoscopic urological surgeries. From January 2005 to December 2013, 4,380 cases of laparoscopic urological surgeries were recruited in our department. The distribution, incidence, and characteristics of intraoperative serious complications were retrospectively sorted out and analyzed. The surgeries were divided into three groups: very difficult (VD), difficult (D), and easy (E). The complication at Satava class II was defined to be serious. One hundred thirty one cases with intraoperative serious complications were found (3.0%). The incidence of these complications was significantly increased along with the difficulty of the surgeries (P<0.05). The highest morbidity of serious complication belonged to total cystectomy with a ratio of about 17% as compared with other surgeries (P<0.05). The types of these complications included small vascular injury demanding blood transfusion (101 cases, 77.1%), large vascular (venous and artery) injury (16 cases), hypercapnia & acidosis (8 cases), and organ injury (6 cases). The cases of conversion to open surgery were 37 (≤1%). There was no significant difference in the rates of conversion to open surgery among the three groups (P>0.05). The overall tendency of the intraoperative serious complications was decreasing with the time from 2005 to 2013. In conclusion, through standardized training including improving the surgical technique, being familiar with the anatomic relationship, and constantly summarizing the experience and lessons, laparoscopic surgery could be safe and effective with not only minimal invasion but also few complications.

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INTRODUCTION

Minimally invasive surgery is more and more popular in the field of surgery, where in especially, laparoscopic surgery is a representative one. It is well known that the benefits of laparoscopic surgery are obvious. At present, the indication of laparoscopic surgery has covered all aspects of urology surgery for its extremely obvious advantages. However, in the awake of the broadening of its indications and then extensive application, the operation number and the difficult surgeries such as highly challenged urology reestablishment and/or destruction are continuously increasing. Mo-
Moreover, the spatial horizon is always limited during the operation. Thus the occurrence of some intraoperative complications with varying degrees may be inevitable. Generally, slight complications such as peritoneal injury and pneumoderm will not cause grave consequences. However, as for some serious complications including the hemorrhage of major abdominal vessels and organ injury, if treated improperly, patients may die (1). A meta-analysis focusing on the carcinoma of urinary bladder treatment by peritoneoscopy and radical cystectomy suggested that laparoscopic surgery with less complication would give rise to smaller positive rate of incisal edge and faster postoperative recovery (2). Therefore, the full understanding of the occurrence characteristics and treatment methods of intraoperative complications will promote the avoidance of the complications as far as possible and enhance the success rate and effectiveness of the operation in the future. However, it is yet not well disclosed up to now. In this study, we analyzed the intraoperative serious complications of 4380 cases of laparoscopic urological surgeries. These cases were completed in our hospital from Jan 2005 to Dec 2013. The intraoperative serious complications were defined by Satava hierarchy system (3): the fault without harmful consequence or negligible fault was evaluated as class I and the fault that was immediately identified and corrected was assessed as class II. Meanwhile, with reference of Inoue et al.’s definition (4), Satava class II was defined as serious complication.

**MATERIALS AND METHODS**

**Clinical information**

From Jan 2005 to Dec 2013, 4380 cases of laparoscopic urological surgeries were recruited in our department. The study protocol was reviewed and approved by the Institutional Ethics Committee, the First Affiliated Hospital of Nanchang University, China. All patients had signed written informed consent forms. The operative types and intraoperative serious complications were retrospectively sorted out and analyzed.

According to European scoring system (ESS) (1), the laparoscopic urological surgeries were divided into three groups: very difficult (VD), difficult (D), and easy (E), based on the complexity of the surgery. Thereinto, the group VD included total cystectomy, radical prostatectomy, and partial nephrectomy; the group D was composed of radical resection of renal carcinoma, adrenal tumorectomy, ligation of renal lymphatic vessel, simple nephrectomy, dismembered pyeloplasty, and radical resection of renal pelvic carcinoma; renal cyst decortication was incorporated into the group E. Some other unusual or ambiguously diagnosed surgeries with great variations and varied difficulty such as ureterolysis of retroperitoneal fibrosis and laparoscopic exploration were incorporated into one of the above groups as other surgeries based on the finally defined difficulty. The intraoperative complications were defined on the basis of Satava hierarchy system (3): the fault without harmful consequence or negligible fault was evaluated as class I and the fault that was immediately identified and corrected was assessed as class II. Meanwhile, with reference of Inoue et al.’s definition (4), Satava class II was defined as serious complication.

**Statistical analysis**

All data were analyzed by using a SPSS 17.0 software (SPSS, Chicago, IL, USA). Difference was justified to be significant at $P < 0.05$.

**RESULTS**

**General information**

The general information of the total 4380 cases and the 131 cases with intraoperative serious complications are shown in Table-1. Effective measures were adopted during the operation, so no adverse effects were found during the perioperative period. We found the incidence of intraoperative serious complications was approximately 3%. Most cases that received laparoscopic urological surgeries were male and the proportion was nearly 2/3. However, the difference in incidence of intraoperative serious complications between genders decreased. As compared with the total cases, the average age of patients with intraoperative serious complications was obviously older. Although the average total length of stay between the total cases...
and the cases with intraoperative complications was similar, the average postoperative length of stay in the cases of intraoperative serious complications was remarkably increased by about 4 days. As was expected, both the intraoperative bleeding volume and operative duration were obviously elevated when the intraoperative serious complications occurred.

Intraoperative serious complications among various groups

The incidence of intraoperative serious complications in the E, D, and VD groups are demonstrated in Figure-1. We revealed that the difficult surgery rather than the easy and very difficult ones was most common. The incidence of intraoperative serious complications was significantly increased along with the difficulty of the surgeries, which was analyzed by chi-square test ($P < 0.05$).

Intraoperative serious complications among diverse surgical procedures

The intraoperative serious complications among diverse surgical procedures are demonstrated in Table-2. The highest morbidity of serious complication belonged to total cystectomy with a ratio of about 17% as compared with other surgeries ($P < 0.05$). In the next place, radical resection of renal pelvic carcinoma and radical prostatectomy suffered relatively high ratio of serious complications (5-10%). The types of these complications are shown in Figure-2. There were small vascular injury, hypercapnia & acidosis, large vascular (venous and artery) injury, and organ injury. The overwhelming majority of complications were small vascular injuries demanding blood transfusion with a percentage of 77.1%. Venous injuries including postcava injury (6 cases), renal vein injury (3 ca-

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**Table 1 - General information of the total cases and 131 cases with intraoperative serious complications.**

<table>
<thead>
<tr>
<th></th>
<th>Total cases</th>
<th>Cases of intraoperative complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>4,380</td>
<td>131 (3.0%) a</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2801 (63.9%)</td>
<td>Male 95 (3.4%) b</td>
</tr>
<tr>
<td>Female</td>
<td>1579 (36.1%)</td>
<td>Female 36 (2.3%) b</td>
</tr>
<tr>
<td>Age</td>
<td>9-88 (Average 49.7)</td>
<td>18-82 (Average 57.2)</td>
</tr>
<tr>
<td>Total length of stay (days)</td>
<td>4-85 (Average 15.2)</td>
<td>7-85 (Average 14.7)</td>
</tr>
<tr>
<td>Postoperative length of stay (days)</td>
<td>1-75 (Average 6.4)</td>
<td>4-75 (Average 10.3).</td>
</tr>
<tr>
<td>Intraoperative bleeding (mL)</td>
<td>2-3000 (Average 61)</td>
<td>50-3000 (Average 653)</td>
</tr>
<tr>
<td>Operative duration (min)</td>
<td>7-840 (Average 74)</td>
<td>70-840 (Average 291)</td>
</tr>
</tbody>
</table>

a Values in the bracket represented the ratio to the total cases. b Values in the bracket represented the ratio to the corresponding total cases of male or female.
ses), and external iliac vein injury (3 cases) were found. The artery injuries were comprised of 1 case of aorta abdominalis injury, 2 cases of renal artery, and 1 case of external iliac artery injury. Organ injuries included 1 case of spleen injury, 3 cases of pleural injury, and 2 cases of mild rectal injury. The last 8 cases of complications were hypercapnia & acidosis.

Intraoperative conversion to open surgery among various groups

As shown in Table-2, the cases of conversion to open surgery were 37 and its percentage was less than 1%. Among them, 22 cases resulted from the complications and the other 15 cases were related to surgical difficulty. The intraoperative conversion to open surgery among VD, D, and E groups are summed in Table-3. By statistical analysis, there was no significant difference in the occurrence rates of the intraoperative conversion to open surgery among the VD, D, and E groups (P>0.05).

Rates of intraoperative serious complications and cases of laparoscopic urological surgeries by the year are depicted in the Figure-3. We could observe that the cases of laparoscopic urological surgeries gradually increased with the time, but the overall tendency of the intraoperative serious complications

<table>
<thead>
<tr>
<th>Groups</th>
<th>Surgical procedures</th>
<th>Total cases</th>
<th>Cases of conversion to open surgery</th>
<th>Intraoperative serious complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD</td>
<td>Total cystectomy</td>
<td>154</td>
<td>2</td>
<td>26 (16.9%)*</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>232</td>
<td>0</td>
<td>14 (6.0%)</td>
</tr>
<tr>
<td></td>
<td>Partial nephrectomy</td>
<td>280</td>
<td>4</td>
<td>8 (2.9%)</td>
</tr>
<tr>
<td></td>
<td>Other surgery</td>
<td>87</td>
<td>1</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td></td>
<td>Radical resection of renal pelvic carcinoma</td>
<td>152</td>
<td>3</td>
<td>15 (9.9%)</td>
</tr>
<tr>
<td></td>
<td>Radical resection of renal carcinoma</td>
<td>606</td>
<td>10</td>
<td>24 (4.0%)</td>
</tr>
<tr>
<td></td>
<td>Dismembered pyeloplasty</td>
<td>228</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Adrenal tumorectomy</td>
<td>713</td>
<td>9</td>
<td>21 (2.9%)</td>
</tr>
<tr>
<td>D</td>
<td>Ligation of renal lymphatic vessel</td>
<td>368</td>
<td>2</td>
<td>8 (2.2%)</td>
</tr>
<tr>
<td></td>
<td>Simple nephrectomy</td>
<td>340</td>
<td>4</td>
<td>6 (1.8%)</td>
</tr>
<tr>
<td></td>
<td>Ureterolithotomy</td>
<td>305</td>
<td>1</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td></td>
<td>Spermatic vein ligation</td>
<td>170</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Other surgery</td>
<td>152</td>
<td>1</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>E</td>
<td>Renal cyst decortication</td>
<td>518</td>
<td>1</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td></td>
<td>Other surgery</td>
<td>75</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total 4,380 37 (0.8%) 131 (3.0%)

Values in the bracket represented the ratio to the cases of corresponding surgical procedures. European scoring system (ESS): VD = very difficult; D = difficult; E = easy; * P < 0.05 vs. other surgeries by chi-square test.
decreased with the time. The occurrence rate of the intraoperative serious complications was smallest in 2013 (1.3%). However, relatively large rates of the intraoperative serious complications over 4.5% were found in 2008 and 2009.

**DISCUSSION**

It is obvious that the incidence of the complications is elevated along with the difficulty increase of the laparoscopic surgery. According to ESS (1), the laparoscopic surgeries are divided into VD, D, and E groups based on the complexity of the surgery. Our results suggested that the VD group including total cystectomy and radical prostatectomy exhibited the highest incidence of intraoperative serious complications, which was followed by the D and subsequent E group. Their incidence during total cystectomy was apparently higher than other surgeries. The procedures of urology reestablishment and/or destruction with high challenge were complicated. Furthermore, the complicate anatomy and great operative difficulty were bound to high incidence of operative serious complications.

Plenty of small vascular injuries demanding blood transfusion were found. In the early stage, the unfamiliarity with anatomy and operation caused blood oozing of the wound, or the conversion to open surgery, and needed blood transfusion. After the surgical technique was matured, these complications were mainly originated from the surgical adhesion, the abundance of tumor surface vessels, and the main position of difficult surgery.

During the laparoscopic renal and adrenal surgeries in the D group, postcava injury was the most common vascular injury. In this study, 6 cases of postcava injury were originated from radical nephrectomy and ligation of renal lymphatic vessel. These vascular wall avulsions of postcava mainly resulted from the operation mistakes and all the avulsions were located in the junction of renal veins and postcava.

Pelvic lymphadenectomy in the total cystectomy or radical prostatectomy easily damage iliac vessels and abdominal vessels (5). In this study, 6 cases of postcava injury were originated from radical nephrectomy and ligation of renal lymphatic vessel. These vascular wall avulsions of postcava mainly resulted from the operation mistakes and all the avulsions were located in the junction of renal veins and postcava.

Table 3 - The sum of the intraoperative conversion to open surgery among VD, D, and E groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Group VD</th>
<th>Group D</th>
<th>Group E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>753</td>
<td>3034</td>
<td>593</td>
</tr>
<tr>
<td>Cases of conversion to open surgery</td>
<td>7</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Occurrence rate</td>
<td>0.9%</td>
<td>1.0%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

European scoring system (ESS): VD = very difficult; D = difficult; E = easy. The difference in the occurrence rates of the intraoperative conversion to open surgery among the VD, D, and E groups was not significant (P > 0.05).

Figure 3 - The intraoperative serious complications and total cases by the year from 2005-2013.
nodes with external iliac vein, the external iliac vein was carelessly lancinate when we dissociated the lymph nodes. One was urgently converted to open surgery and the other one was sutured under a laparoscope. There were diverse reasons for the large vascular injury during the laparoscopic surgery (6): Firstly, the laparoscopic anatomy was lack of understanding; secondly, overexertion or misoperation might induce unforeseen circumstances; thirdly, anatomic variation or local dysplasia might be the disadvantage as well; last, surgical adhesion would increase the operative difficulty. The laparoscopic treatments of large vascular injury were recommended as follows: Hemostasis by clamping or pressing, appropriate dissociation of perivascular tissues to occlude blood vessels, suture like number 8 with 4-0 atraumatic suture, and clamping of blood vessels by using vascular clamp. However, the most important issue was to prevent large vascular injury. The surgeons were required to be very familiar with local anatomy. The location of the main vessels must be well understood. Preoperative computed tomography angiography should be performed to understand individual vascular differences. The dissociation should be moved gently along the running direction of the vessels as far as possible.

If the definite hemorrhage of large blood vessels and inability to form a visible environment or to create an operating environment were found, patients should be converted to open surgery. If excessive bleeding was from the tumor vessels, or vessels at unclear location and the bleeding could not be effectively stopped in a short time, patients should be converted to open surgery as well.

Rectal injury was the most serious intraoperative complication in the radical prostatectomy (6). History of prostate surgery, abdominal surgery, perineal operation, radiotherapy, or castration would augment the surgical difficulty and the subsequent occurrence of complications (7). Here, two cases of rectal injury were found in the 232 cases of radical prostatectomy (0.9%). Guillonneau et al. retrospectively analyzed 1000 cases of laparoscopic radical prostatectomy and altogether 13 cases of rectal injury took place (1.3%) (8). Guillonneau thought that rectal injury was likely to take place in two procedures. First, when operators dissociated the plane between Denonvillier’s fascia on the prostate apex and the rectum, it might happen by reason of the near location of Denonvillier’s fascia to the rectum, small dissociation gap, and especially the existence of tumor infiltration or preexistent envelope perforation of transurethral resection of the prostate. Besides, when the Denonvillier’s fascia was incised, the rectum might be injured on account of the excessive adjacency of the incision to the rectum and the distant location of the incision to pars basilaris of seminal vesicle behind the prostate. The dissociation at right anatomical level played a crucial role in the prevention of rectal injury. When dissociating the Denonvillier’s fascia, surgeons should use the gap of fat layer in front of the rectum as marks. Sharp dissection is recommended to reduce the risk of rectal injury. Intraoperative electric injury which would produce postoperative intestinal fistula was often neglected. The overuse of BiClamp to stop the bleeding of the rectal antetheca should be avoided. Before operation, bowel preparation should be improved and during operation, special attention should be paid to whether there is rectal injury after the separation of the prostate and rectum.

Spleen injury is occasionally reported in renal and adrenal surgeries and its incidence rate is about 0-2.5%. Tractive operations of the upper pole of left kidney and left adrenal surgeries easily can damage the spleen and the dissociation of the upper pole of left kidney damages splenic vein easily (9). Mostly, the pleural injury is secondary to diaphragmatic injury. It is common in surgeries with high operation plane such as adrenal and upper pole of kidney operations (10). After pleura rupture, carbon dioxide rapidly enters into thoracic cavity, leading to pneumothorax. Here, two cases of pleural injury occurred during radical nephrectomy and renal cyst decortication. During operation, the fascia around the upper pole of kidney was tightly adhesive to the fat and it was difficult to perform dissociation. The pleura was ruptured when forcibly dissociated.

In comparison with open surgery, the specific complications of laparoscopic surgery include hypercapnia, acidosis, and the damage induced by puncture cannula. After pneumoperitoneum
establishment, carbon dioxide enters the bodies and patients may suffer hypercapnia and various degrees of acidosis (11). In this study, there were 8 cases of hypercapnia and acidosis which were mostly due to age of patients, long operative time, and hemorrhage during operation. Once severe hypercapnia occurred, surgical procedures should be suspended immediately. Turn off pneumoperitoneum tube and extract intra-peritoneal gas completely by using an aspirator. Furthermore, the operator should enjoin an anesthetist to increase tidal volume. Hypercapnia should be corrected. The surgery could go on until the recovery of some indexes such as oxyhemoglobin saturation of the peripheral blood and carbon dioxide pressure; moreover, low abdominal pressure should be maintained and the surgery should be finished as soon as possible (12). Cannula insertion is indispensable to laparoscopic surgery and it is also the first step of the surgery. Serious complications related to the cannula insertion stage are reported sometimes. The cannula shall be inserted by direct incision as far as possible. First cannula is inserted directly through the incision and other cannulas are inserted under direct vision, which can effectively reduce this kind of complications.

Here, the incidence of intraoperative serious complications reached peak value in 2008, which was associated with the extensive development of a large number of highly difficult laparoscopic surgeries including total cystectomy and the operator change of laparoscopic surgeries from a few experts to a lot of fresh professionals in our department since 2007. Hereafter, the incidence of intraoperative serious complications declined year by year, which was connected with the accumulation and proficiency of the operation and conformed to the learning curve and regularity of laparoscopic surgeries.

Although there are still a variety of unpredictable complications in retroperitoneal laparoscopic surgery, the operation time and complication rate will be certainly and greatly reduced with the continuous improvement of surgical technique. The indications of laparoscopic surgery shall be strictly controlled and the microscopic structure shall be clearly understood during operation, so as to avoid accidental injury of peritoneum and abdominal organs. These complications can be reduced or avoided by improving the surgical technique, being familiar with the anatomic relationship, and constantly summarizing the experience and lessons. Only in this way can we give full play to the advantages of minimally invasive surgery.

In summary, the occurrence of intraoperative serious complications was associated with the laparoscopic technique, the grasp of anatomy, and the difficulty of operation. Vascular and visceral injuries could be repaired by laparoscopic or open surgery according to objective conditions and the prognosis was satisfying. Through standardized training, laparoscopic surgery could be safe and effective with not only minimal invasion but also few complications.

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Ju Guo, Zhigang Zeng, contributed similarly as first author

CONFLICT OF INTEREST

None declared.

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Challenging risk factors for right and left laparoscopic adrenalectomy: A single centre experience with 272 cases

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ABSTRACT

Purpose: This study aimed to compare perioperative and postoperative results of right and left laparoscopic adrenalectomy (LA), and to evaluate the impact of challenging factors on these outcomes.

Materials and Methods: A total of 272 patient’s medical records that underwent single side LA between October 2006 and September 2017 were retrospectively reviewed. The patients were divided into 2 groups according to operation side. Moreover, pheochromocytoma, metastatic masses and adrenal lesions >5cm in size were considered to be difficult adrenalectomy cases and the outcomes of these cases were compared between two groups.

Results: 135 patients (49.6%) underwent right LA and 137 patients (50.4%) underwent left LA. Operation time, estimated blood loss (EBL) and hospitalization time were similar between the groups (p=0.415, p=0.242, p=0.741, respectively). Although EBL was higher on the right side than the left (p=0.038) in the first 20 cases, after this learning period has been completed, there was no significant difference between the groups. In patients with pheochromocytoma, metastatic mass and a mass >5cm in size, despite bleeding complications were clinically higher on the right side, this difference was not statistically significant.

Conclusions: During the learning period of LA, EBL is higher on the right side. Due to the greater risk of bleeding complications on the right side even on the hands of experienced surgeons, extra care and preoperative planning are required in patients with pheochromocytoma, metastatic masses and masses >5cm in size.

INTRODUCTION

The laparoscopic treatment of adrenal masses was first described by Gagner et al. in 1992 (1). When compared with open adrenalectomy (OA), laparoscopic adrenalectomy (LA) is known to have better cosmetic results in addition to less blood loss and a shorter length of stay in hospital (2, 3). Despite current controversy in the laparoscopic surgery of large and metastatic adrenal masses, LA has become the standard surgical method for benign adrenal masses (4, 5).

Both of the adrenal glands have different anatomical features. The right adrenal gland has a partial retrocaval localisation, is adjacent to the liver and duodenum and drains to the inferior vena cava (6, 7). It has been reported that LA on the right side could be more difficult because
of these differences between the two sides (6, 7). Although there are few studies in literature that have compared adrenalectomy on both sides, different interpretations can be seen in these studies. In this article, considering our large clinical data, we compared the perioperative and postoperative results of right and left LA. Moreover, herein we firstly evaluated the challenging factors, such as surgical experience and histopathological properties on these outcomes.

MATERIALS AND METHODS

Between 2006 and 2017, data of patients submitted to LA in our clinic were retrospectively reviewed. Patients were excluded if they underwent bilateral LA, had a history of surgery for the same reason, or had a bleeding diathesis or a skeletal deformity. The patients were separated into 2 groups; Group 1 comprised cases submitted to right-side LA, and Group 2 comprised cases submitted to left-side LA.

In accordance with the recommended guidelines, surgery was performed to adrenal lesions expressing hormone with clinical importance, non-functioning lesions that were determined radiologically to have a risk of malignancy and lesions showing a tendency for growth (8, 9). All the operations were performed with a lateral transperitoneal approach method by 3 different surgeons.

The groups were compared in respect of age, gender, mass size, operating time, estimated blood loss (EBL), length of stay in hospital and complications. The measurement in the pathology report was taken as the mass size. The operating time was calculated as the time from entry of the camera and working portals to closure of the incision after removing the mass from the body. EBL was measured by collecting the postoperative drainage amount and subtracting the amount of fluid irrigation from the amount aspirated during the operation.

Based on the previous studies, the first 20 cases in the series were accepted as the learning period and the data of this period were compared to the results of these cases were compared separately for the two groups.

Data obtained in the study were analysed statistically using SPSS v 22 software (Chicago, IL, USA). Categorical data were compared using the Chi-square test. Quantitative data were compared using the Independent Samples t-test and the Mann Whitney U-test. A value of p <0.05 was accepted as statistically significant.

RESULTS

Totally 272 patients were analysed, comprising 107 (39.3%) males and 165 (60.7%) females. Group 1 included 135 (49.6%) cases of right-side LA, and Group 2 included 137 (50.4%) cases of left-side LA. No statistically significant difference was determined between the groups in terms of age, gender, operating time, EBL, mass size, and length of hospital stay (p=0.888, p=0.130, p=0.415, p=0.242, p=0.184, p=0.741 respectively) (Table-1).

Considering the first 20 cases as in the learning period, comparisons of the right and left LA of these cases are shown in Table-2. Although the differences were not statistically significant, the mean operating time on the right side was longer than the left side (p=0.766). However, the size of the adrenal mass on both sides was similar, the mean estimated blood loss (EBL) was statistically significantly higher on the right side (55.5±19.2mL) than on the left side (41.1±7.8mL) (p=0.038) (Table-2). After this learning process has been completed, there was no significant difference regarding EBL.

The results of the 41 patients submitted to right and left LA because of pheochromocytoma were found to be similar (Table-2). The EBL of the right-side LA was greater than that of the left side, but not to a statistically significant level (75.2±98.4mL vs. 51.1±22.2mL) (p=0.386) (Table-2). In 1 patient (case no: 80) submitted to right LA because of a 5cm right-side adrenal pheochromocytoma, 1 unit erythrocyte (ES) replacement was administered perioperatively because of 500cc blood loss.

No significant difference was determined between the patients submitted to right
and left LA because of the pathology report of metastasis (Table-2). The EBL was found to be 79.6±75.7mL in the right side and 47.2±38.8mL in the left-side operations (p=0.148) (Table-2).

The results of the patients submitted to right and left LA because of adrenal mass >5cm were found to be similar (Table-2). The EBL of the right-side LA surgeries for mass >5cm in size was greater than that of the left side but not to a statistically significant level (80.6±88.3mL vs. 52.6±40.6mL) (p=0.106) (Table-2). Open conversion was employed in one

| Table 1 - Comparison of right and left laparoscopic adrenalectomy cases. |
|-------------------------------------------------|-----------------|-----------------|---|
| Right Side (n:135) | Left Side (n:137) | P value |
| Age | | | |
| Mean (sd) | 51±11.7 | 50.7±11.8 | 0.888t |
| Median (range) | 51 (24-82) | 50 (21-88) | |
| Gender | | | |
| Male | 47 (34.8%) | 60 (43.8%) | 0.130ch |
| Female | 88 (65.2%) | 77 (56.2) | |
| Operation Time (min) | | | |
| Mean (sd) | 98.7±36.6 | 100.6±33.2 | 0.415m |
| Median (range) | 90 (45-210) | 92 (40-210) | |
| Estimated Blood Loss (mL) | | | |
| Mean (sd) | 59.3±61.2 | 47±27.5 | 0.242m |
| Median (Range) | 50 (100-500) | 50 (10-200) | |
| Mass Size (mm) | | | |
| Mean (sd) | 41.4±19 | 39.2±19.3 | 0.184m |
| Median (range) | 40 (10-150) | 35 (10-100) | |
| Pathology | | | |
| Adenoma | 72 | 68 | |
| Pheochromacytoma | 22 | 19 | |
| Adrenocortical Carcinoma | 5 | 2 | |
| Metastasis | 14 | 20 | |
| Leomyosarcoma | 1 | 0 | |
| Malign Pheochromacytoma | 1 | 0 | |
| Other Benign | 20 | 28 | |
| Hospital Stay (day) | | | |
| Mean (sd) | 2.9±1.5 | 2.9±2.4 | 0.741m |
| Median (range) | 3 (1-8) | 2 (1-26) | |

t = Independent Simple Test; m = Mann-Whitney u Test; n = Number; sd = Standard Deviation
Table 2 - Comparison of challenging right and left laparoscopic adrenalectomy cases.

<table>
<thead>
<tr>
<th></th>
<th>Right Side</th>
<th>Left Side</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± sd</td>
<td>Min-Max (Median)</td>
<td>Mean ± sd</td>
</tr>
<tr>
<td><strong>First 20 Cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong>: (Right:11 / Left:9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52.2±8.3</td>
<td>37-68 (50)</td>
<td>47.7±11</td>
</tr>
<tr>
<td>Operation Time (min)</td>
<td>160±36.6</td>
<td>120-210 (180)</td>
<td>154.4±36.1</td>
</tr>
<tr>
<td>Estimated Blood Loss (mL)</td>
<td>55.5±19.2</td>
<td>30-100 (50)</td>
<td>41.1±7.8</td>
</tr>
<tr>
<td>Mass Size (mm)</td>
<td>33.6±11.6</td>
<td>20-60 (32)</td>
<td>35.6±12.4</td>
</tr>
<tr>
<td>Hospital Stay (day)</td>
<td>3.8±1.7</td>
<td>2-7 (3)</td>
<td>3±1</td>
</tr>
<tr>
<td><strong>Pheochromocytoma</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>n</strong>: (Right:22 / Left:19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>49.1±14.4</td>
<td>24-75 (50.5)</td>
<td>42.8±13.3</td>
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<td>Operation Time (min)</td>
<td>106.6±42.6</td>
<td>45-210 (97.5)</td>
<td>118.7±33.6</td>
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<tr>
<td>Estimated Blood Loss (mL)</td>
<td>75.2±98.4</td>
<td>10-500 (50)</td>
<td>51.1±22.2</td>
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<tr>
<td>Mass Size (mm)</td>
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<td>10-80 (45)</td>
<td>51.3±16.8</td>
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<td>Hospital Stay (day)</td>
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<td>1-6 (3)</td>
<td>2.9±1</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>n</strong>: (Right:14 / Left:19)</td>
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<td></td>
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<tr>
<td>Age</td>
<td>55.5±8.0</td>
<td>41-71 (54)</td>
<td>58.1±9.2</td>
</tr>
<tr>
<td>Operation Time (min)</td>
<td>98.5±27.6</td>
<td>60-150 (95)</td>
<td>100±40.1</td>
</tr>
<tr>
<td>Estimated Blood Loss (mL)</td>
<td>79.6±75.7</td>
<td>25-300 (50)</td>
<td>47.2±38.8</td>
</tr>
<tr>
<td>Mass Size (mm)</td>
<td>38.5±16.7</td>
<td>13-73 (34)</td>
<td>41.3±26.8</td>
</tr>
<tr>
<td>Hospital Stay (day)</td>
<td>2.6±1.3</td>
<td>1-6 (2.5)</td>
<td>4.7±5.3</td>
</tr>
<tr>
<td><strong>Mass Size &gt;5cm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong>: (Right:45 / Left:41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>47.1±12.5</td>
<td>24-71 (46)</td>
<td>48.8±12.8</td>
</tr>
<tr>
<td>Operation Time (min)</td>
<td>106.2±32.9</td>
<td>60-180 (95)</td>
<td>106.1±31.7</td>
</tr>
<tr>
<td>Estimated Blood Loss (mL)</td>
<td>80.6±88.3</td>
<td>10-500 (50)</td>
<td>52.6±40.6</td>
</tr>
<tr>
<td>Mass Size (mm)</td>
<td>61.7±18.2</td>
<td>50-150 (55)</td>
<td>62.6±15.7</td>
</tr>
<tr>
<td>Hospital Stay (day)</td>
<td>2.8±1.3</td>
<td>1-6 (3)</td>
<td>3.3±3.8</td>
</tr>
</tbody>
</table>

* = Independent Simple Test; ** = Mann-Whitney u Test; n = Number; sd = Standard Deviation
patient with diagnosis of 5cm of functional right adrenal adenoma due to excessive bleeding in number of 119th of the series.

DISCUSSION

With the current prominence of minimally invasive treatments, laparoscopic and robotic methods have started to be used in place of open surgery. Following the first description of minimally invasive adrenalectomy, LA started to be considered as a treatment method (1, 11). Laparoscopy is now applied as the standard in the surgical treatment of several pathologies (6). Although different surgical techniques have been described such as anterior, lateral and retroperitoneal approaches, the lateral transperitoneal approach is the most commonly used (7). The most important advantages of the lateral transperitoneal method are that it provides the opportunity to work in a wider surgical area and there is clearer visualisation of the surrounding organs (12).

The vascular properties and the organs around the adrenal glands, which are located in the upper retroperitoneal area, are different on the right and left sides. Due to these anatomic differences between the right and left adrenal glands, there is an opinion that right-side LA is more difficult than left-side (6, 7, 13). Moreover, there are different interpretation in studies in literature that have compared the perioperative data of right and left LA. Although right-side surgery has been reported as shorter in some series made with an anterior approach there are also studies that have emphasised that the operating time is similar on both sides (14, 15). In cases submitted to the transperitoneal method, Reider et al. reported that right-side surgery was shorter and tended to be less bleeding on the right side (6). Although Cianci et al. found the operating time to be longer on the left side in cases submitted to the lateral transperitoneal method, it was emphasised that left side surgery was more complex (7). The longer operating time on the left side was associated by both of these authors with renal hilus dissection and mobilisation of the spleen and splenic colonic flexure during adrenalectomy. In the current study, the operating times and blood loss values were found to be similar on both sides (Table-1). This shows that when the surgeon is sufficiently experienced, renal hilus dissection and mobilisation of the spleen and splenic colonic flexure, which are thought to make left-side surgery more complex, can be applied quickly and without problems.

Although there are different views in literature related to the LA learning curve, Higashihara et al. reported this period to be 20 cases (10, 16–19). In the first 20 cases of the current series, despite larger-sized left-side masses, the amount of bleeding was greater in right-side operations, but this difference was eradicated as the number of cases increased (Table-2). This shows that in adrenalectomies performed before sufficient experience is acquired, there is a greater possibility of bleeding from the right side, even if the mass is of small dimensions, and when a certain level of experience is reached, the bleeding risk on the right side was seen to decrease.

Even for experienced surgeons, laparoscopic surgery of pheochromocytoma has been reported to be more difficult than other adrenal lesions (20). In addition, surgery of metastatic lesions may be more difficult because of adhesions to surrounding tissues, and masses >5cm have been reported to constitute a risk for conversion of laparoscopy to open surgery (21). Despite the similarity of preoperative results and length of hospital stay of the adrenalectomy cases in the current study with this difficult adrenalectomy cases, it was noticeable that the mean amount of bleeding was greater from the right side than from the left in all three groups (Table-2). Furthermore, as the cases with bleeding requiring ES replacement and the one case that was converted to open surgery were on the right side, this showed that right-side LA could be more dangerous than left-side LA in difficult adrenalectomy cases. However, experienced the surgeon is, if surgery is performed because of a pheochromocytoma, metastasis or a mass >5cm, on the right side, more care must be taken. It is also important that in these difficult cases where there is the possibility of sudden bleeding, the anaesthetist must be warned for a broad vascular route or central catheterisation to be able to make the necessary rapid intervention and the operation should only be started after the preoperative preparation of ES.
With the exception of patients submitted to bilateral adrenalectomy, all patients submitted to LA were included in the study. Therefore, there was no selection bias in this study. However, that the study was retrospective and that the operations were performed by 3 different surgeons, albeit of similar experience, can be considered limitations of the study.

CONCLUSIONS

In conclusion, although the adrenal glands show different anatomic features on the right and left sides, after acquiring a certain level of experience, the results of right and left LA are similar and the operations have an equal degree of difficulty. However, as there is a greater risk of bleeding during right-side LA performed in the learning period, right-side LA can be said to be more difficult for a surgeon at this stage. Furthermore, even for experienced surgeons, as there is a greater risk of bleeding on the right side, extra care and preoperative planning are required for pheochromocytoma, metastatic masses and masses >5cm in size.

ABBREVIATIONS

LA = Laparoscopic adrenalectomy
OA = Open adrenalectomy
EBL = Estimated blood loss

CONFLICT OF INTEREST

None declared.

REFERENCES


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Study of kidney morphologic and structural changes related to different ischemia times and types of clamping of the renal vascular pedicle

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1 Hospital Israelita Albert Einstein, São Paulo, Brasil; 2 Laboratório de Urologia, Faculdade de Medicina da Universidade São Paulo – USP, SP, Brasil; 3 Disciplina de Nefrologia, Escola Paulista de Medicina, Universidade Federal de São Paulo – Unifesp, SP, Brasil

ABSTRACT

**Purpose:** This study aimed to study morphological and renal structural changes in relation to different ischemic times and types of renal vascular pedicle clamping.

**Methods:** Sixteen pigs were divided into two groups (n = 8): Group AV - unilateral clamping of the renal artery and vein and Group A - unilateral clamping of the renal artery only, both with the contralateral kidney used as control. Serial biopsies were performed at 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90 minutes after clamping.

**Results:** There is a correlation between the occurrence of renal damage as a function of time (p <0.001), with a higher frequency of Group A lesions for cellular alterations (vascular congestion and edema, interstitial inflammatory infiltrate, interstitial hemorrhage and cell degeneration), with the exception of in the formation of pigmented cylinders that were evidenced only in the AV Group.

**Conclusion:** The number of lesions derived from ischemia is associated with the duration of the insult, there is a significant difference between the types of clamping, and the AV Group presented a lower frequency of injuries than Group A. The safety time found for Group A was 10 minutes and for Group AV 20 minutes.

ARTICLE INFO

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INTRODUCTION

Nephron-sparing renal surgery with renal ischemia (partial nephrectomy) is the gold standard technique, during which it is observed blood flow interruption to the vascular pedicle in order to reduce intra-operative bleeding and to ease dissection. Kidneys, differently of other organs, endure lack of up to 20% of their blood flow. However, patients submitted to this procedure may develop acute transitory renal failure (that may last days, hours or even weeks). It also can cause definitive failure (1, 2).

There are two paradigms related to renal ischemia (RI). First, safety time to induce ischemia without harming renal function. Different values are reported, with a safety window varying from 25, 30 to 60 minutes. Some authors suggest a safety
window of 25 minutes, while others report 30 or 60 minutes (3, 4). The second paradigm is associated to the type of clamping used to interrupt blood flow (5). Some authors recommend clamping only the renal artery, causing less harm to the kidney due to the presence of venous flow. Other studies suggest that clamping all renal vascular pedicle may result in lower number of renal lesions following surgery (6, 7).

Most studies using experimental models of ischemia-reperfusion collect samples before and after the surgical procedure (hours or even days) (8). Differently than the reference articles, the appointed study was made “in loco”, collecting renal parenchyma samples in timely intervals, in order to map histological alterations according to time (length) of renal ischemia. Pigs were used as experimental animals due to their anatomic and physiologic similarities to human kidney.

In the present study, we checked the main renal histological alterations according to different times of ischemia and types of clamping in pigs, in order to verify safety time for renal ischemia and significant differences between clamping techniques.

MATERIAL AND METHODS

Pigs

Large white female pigs two months old, weighting 25 to 30 kg, were used. This project was approved by the Ethical and Animal Experimentation Committee of the Hospital Israelita Albert Einstein, São Paulo, Brazil, protocol #2617.

Study design

Sixteen pigs were used, divided in two major study groups: AV group (artery and vein) and A group (artery), distributed in 8/16 each: the right kidney was the control (no clamping) and the left kidney the experiment (clamped). Meaning that clamping was unilateral in both groups. Biopsy samples were collected timely at 0, 10, 20, 30, 40, 50, 60, 70, 80 and 90 minutes of clamping in each of the major study groups, bilaterally. Samples were kept in vials containing buffered formaldehyde 10% that were posteriorly processed and blocked in paraffin. Slices of 3μm were obtained and stained with HE technique (hematoxylin-eosin) and were analyzed at the optical microscope.

Experimental protocol to induce ischemia

Animals were sedated via intramuscular with an injection of ketamine (10mg/kg body weight) and midazolam (0.25mg/kg body weight). After 15 minutes, a catheter caliber 20 or 22 (BD Insystem, BectonTherapy Systems Inc., USA) was inserted in the marginal vein of right ear to induce anesthesia with thiopental (7mg/kg body weight). Fastening was balanced with an initial dose of 2mL/kg/hour of rapid crystalloids and maintained with 10mL/kg/hour during surgical procedure. For endotracheal intubation it was used tubes 6.5 to 8.5 diameter (Portex®). Likewise, hypoxia was induced lowering oxygen inspired flow to 0.06-0.0, and anesthesia was maintained with inhaling isoflurane 2%. At the same time, current volume of 10mL/kg was maintained and analgesia was maintained with fentanyl (2-5mg/kg). Each animal was submitted to hemodynamics monitoring with invasive arterial pressure, heart rate and oxygen level. The anesthetized animal was kept in horizontal dorsal decubitus, local hygiene and with surgical fields with non-sterile technique. A midline abdominal incision was made to evaluate the kidneys with easy handling via retroperitoneal. Open surgical technique was chosen to access both kidneys (simultaneously) since laparoscopy does not allow for this procedure. Although bilateral, laparoscopy is not performed simultaneously (needing right and left lateral decubitus). With this approach, the right kidney (control) and the experimental (left kidney) would be approached simultaneously in each animal, lowering the number of animals needed. Next, left renal pedicle (AV group) and renal artery (A group) were clamped with a bulldog vascular clamp for 90 minutes, during which time the serial renal parenchyma biopsies, in the appointed times, were collected, using a scalpel #11. Biopsies were standardized in 1x1cm² in the cortical region. After each biopsy, the local was compressed with gauze to control bleeding, that did not need any extra procedure for control (kidney pigs show a good hemostatic response). Serial biopsies did not affect negatively the kidneys, since they were performed at the cortex.
in different locals. After 90 minutes surgical clamps were removed, and in the end of the surgical procedure the animals were euthanized under general anesthesia with an overdose of thiopental and potassium chloride 19.1% IV (dose 15-30mg/kg).

Experimental results

Ischemia effects were observed by histopathological qualitative analysis. The presence or absence of histological changes (frequency and prevalence) were compared between study groups according to time and type of clamping.

Described cellular alterations included: (a) degenerative alterations and vacuolization of tubular cells; (b) presence of pigmented cylinders; (c) vascular congestion; (d) edema; (e) interstitial neutrophilic infiltrate; and (f) interstitial hemorrhage.

Statistical analysis

Results are presented in proportions, standard errors and 95% confidence intervals obtained by general estimative equation model (GEE) with binomial distribution.

Also, several multiple comparisons of medium values were made using the sequential Bonferroni test, using the SPSS software (IBM Corp. 2016). P <0.05 was considered statistically significant (9).

RESULTS

In this study, we used a non-lethal model of renal lesion and no animal or data were excluded during analysis.

Histological results

Forty biopsies were collected to analyze histologically each of the studied groups: Groups A and AV, n=10/20 kidney control and n=10/20, experimental kidney for each group.

Five tissue lesions were identified at renal biopsies: vascular congestion and edema, interstitial inflammatory infiltrate, degenerative alteration of tubular epithelial cells, pigmented cylinders and interstitial hemorrhage (Figure-1). However, in some instances, all biopsies in some of the groups showed determined lesion or any of them or in any group had any lesion. Therefore, it was not possible to evaluate the effects in the proposed times and groups using inferential methods or hypothesis tests.

Presence of vascular congestion and edema was observed in 90% of biopsies of ischemic kidney and 76.5% of control kidneys in Group-A. However, in AV Group, such lesions were present in 63.8% of ischemic kidney biopsies and 52.5% of control kidneys.

Tubular degenerative alterations (luminal dilatation, cytoplasm vacuolization, loss and peeling of epithelial cells) were observed mainly in proximal twisted tubules. The same alterations were identified in 67.5% of biopsies of ischemic kidneys and in 57.5% of control kidneys in Group A. In relation to AV group, the same was observed in 52.5% of biopsies of ischemic kidneys and in 43.7% of control kidneys.

Pigmented cylinders were observed in 6.25% of biopsies of ischemic kidneys and in none of control kidneys in Group A. In Group AV, the same lesion was seen in 30% of biopsies of ischemic kidneys and in 15% of control kidneys.

Interstitial hemorrhage was observed in 32.25% of biopsies of ischemic kidneys in Group A, and in 38.7% in control kidneys. In group AB, the lesion was observed in 5% of biopsies of ischemic kidneys and in 15% of control kidney biopsies.

Finally, the presence of interstitial inflammatory infiltrate was observed in 30% of biopsies of ischemic kidneys in group A and in 17.5% in control kidneys biopsies. The same alteration was found in relation to the number of cellular alterations in 15% of ischemic kidneys and 5% of control kidneys in Group AV.

The number of cellular alterations according to time and type of clamping is shown in Figure-2.

Time (minutes)

- Artery group (ischemic kidney) Artery group (control kidney);
- Artery and vein group (ischemic kidney) Artery and vein group (control kidney);
Figure 1 - A) Tubular degenerative changes; B) pigmented cylinders; C) vascular congestion and edema; D) interstitial neutrophilic infiltrate; E) interstitial haemorrhage. All histological findings were stained with Hematoxylin-Eosin technique and analyzed under light microscopy.

- Number of biopsies with degenerative alterations of tubular cells;
- Number of biopsies with inflammatory interstitial infiltrate;
- Number of biopsies with interstitial hemorrhage;
- Number of biopsies showing pigmented cylinders;
- Number of biopsies with vascular congestion;

Alterations according to clamping times

Analysis of total number of lesions was made using the General Estimative Equation model (GEE), that considered the total number of observed lesions in each biopsy (variable response), study groups (groups A and AV with respective ischemic and control kidneys-explicative variable) and clamping time (10, 20, 30, 40, 50, 60, 70, 80 and 90 minutes).

Table-1 shows the multiple comparisons among study groups (total number of lesions observed according to clamping time). After 20 minutes (p <0.001), there was a significant increase of the number of lesions, compared to basal time in ischemic kidneys in group A. Likewise, in the control kidneys, it was observed that at 30 minutes (p=0.001), 50 minutes (p <0.001), 70 minutes (p <0.001) and 80 minutes (p <0.001) there was significant increase of the number of lesions in comparison to basal time. On the other hand, in the ischemic kidneys of AV group there was significant increase of the number of lesions compared to basal time at 40 min (p <0.001), 50 min (p <0.001), 60 min (p=0.001), 70 min (p <0.001) and 90 min (p <0.001).

Finally, Table-2 shows the proportion of estimated lesions according to type of clamping; in Group A, after 20 minutes (both experimental
Figure 2 - From left to right, the following cellular changes are observed as a function of the ischemia and type of clamping: degenerative tubular alteration, interstitial inflammatory infiltrate, interstitial hemorrhage, pigmented cylinders and vascular congestion.
### Table 1 - Estimated proportions for the presence of lesion in the biopsies performed.

<table>
<thead>
<tr>
<th>Comparison (min x Basal)</th>
<th>Artery and vein</th>
<th>Artery</th>
<th>Study groups</th>
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<tbody>
<tr>
<td></td>
<td>Control Kidney</td>
<td>Ischemic Kidney</td>
<td>Control kidney</td>
</tr>
<tr>
<td>10</td>
<td>0.555</td>
<td>0.102</td>
<td>0.046</td>
</tr>
<tr>
<td>20</td>
<td>0.137</td>
<td>0.038</td>
<td>0.003</td>
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<tr>
<td>30</td>
<td>0.135</td>
<td>0.004</td>
<td>0.001</td>
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<tr>
<td>40</td>
<td>0.094</td>
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<td>0.003</td>
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<tr>
<td>50</td>
<td>0.008</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60</td>
<td>0.001</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>70</td>
<td>0.019</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>80</td>
<td>0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
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<tr>
<td>90</td>
<td>0.137</td>
<td>&lt;0.001</td>
<td>0.025</td>
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</table>

P values corrected by the sequential Bonferroni method.

### Table 2 - Results of multiple comparisons between moments regarding the presence of lesions using Bonferroni Method with p value <0.001.

<table>
<thead>
<tr>
<th>Basal (min)</th>
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<th>Artery</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control kidney n (%)</td>
<td>Ischemic kidney n (%)</td>
</tr>
<tr>
<td>0</td>
<td>10.0 (3.5)</td>
<td>7.5 (4.9)</td>
</tr>
<tr>
<td>10</td>
<td>7.5 (3.4)</td>
<td>12.5 (4.9)</td>
</tr>
<tr>
<td>20</td>
<td>20.0 (5.0)</td>
<td>25.0 (5.9)*</td>
</tr>
<tr>
<td>30</td>
<td>27.5 (7.0)*</td>
<td>32.5 (4.9)*</td>
</tr>
<tr>
<td>40</td>
<td>27.5 (6.1)*</td>
<td>37.5 (5.5)*</td>
</tr>
<tr>
<td>50</td>
<td>30.0 (5.0)*</td>
<td>37.5 (6.6)*</td>
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<tr>
<td>60</td>
<td>37.5 (8.2)*</td>
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<tr>
<td>90</td>
<td>30.0 (9.4)*</td>
<td>47.5 (7.0)*</td>
</tr>
</tbody>
</table>

*Significant difference in relation to basal time. Data represent estimated proportions and standard errors obtained with the general estimative equation model.
and control kidneys) 20% an 32.5% showed a significant increase of the number of lesions according to the type of clamping, respectively. Also, in group AV, the ischemic kidneys showed after 20 minutes (25%) a significant increase of number of lesions. In kidney controls such increase was observed following 30 minutes (27.5%).

**DISCUSSION**

When we analyze the occurrence of renal lesion only in relation to time, there is an interaction between these two variables (p <0.001): the number of lesions increases proportionally to the ischemia time (Figure-3). These results are coincident with those of literature (10, 11). Samples from ischemic kidneys show higher number of lesions compared to control kidneys.

**Percentage of biopsies with the presence of lesions**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Artery group (ischemic kidney)</th>
<th>Artery group (control kidney)</th>
<th>Artery and vein group (ischemic kidney)</th>
<th>Artery and vein group (control kidney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>90</td>
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</table>

In relation to groups A and AV, most tissue lesions (vascular congestion and edema, tubular degenerative alterations, inflammatory interstitial infiltrate and interstitial hemorrhage) were more prevalent and frequent in Group-A in relation to group AV. Lesions were identified 10 minutes after induction of ischemia in Group-A and after 20 minutes in Group AV. The only alteration with higher prevalence and frequency in Group AV was the presence of pigmented cylinders, particularly in the ischemic kidney after 60 minutes. Based on these results, it was shown a significative difference between the types of clamping of renal pelvis. Early histological alterations were detected when only the renal artery was clamped, suggesting a renoprotective effect, compared to clamping renal artery and vein. These results are in accordance to Thompson et al., that demonstrated that renal artery clamping causes lower grade of renal alterations compared to clamping of renal artery and vein (12). However, our results are opposite of those of Mir et al., that suggested that clamping renal artery and vein during open surgery of pigs causes more harm them the clamping of only the renal artery, and that venous flow would benefit renal homeostasis (13). Chan et al. suggested that arterial clamping must be avoided since it causes vasospasm that are closely related to renal dysfunction (14).

**Figure 3 - Distribution of the proportion of biopsies with presence of lesion.**
In relation to the results of time, data of the AV group (20-30 minutes) are in accordance to those observed at literature, that recommends ischemia time between 25 and 30 minutes (Volpe et al., 5). In humans, there are several studies that considers that kidneys are able to endure 30 to 60 minutes of ischemia, without damaging renal function (15). It is known that renal lesion is to an extension reversible, and the identification of the transition time for irreversibility must still be determined. Variables such as surgical technique, patient’s age, comorbidities such as diabetes and hypertension, arterial vascularization and pre-operative renal function determine that the ischemic damage must be reduced to a minimum, and it is suggested the use of hypothermia after 30 minutes of ischemia (16).

It is important to have in mind that factors such as the maintenance of anesthesia, monitoring blood pressure and hydration are fundamental for hemodynamics stability and reduction of negative effects on renal function (17).

The use of these data must guide the design of clinical trial protocols. In patients with normal pre-operative function, 30 minutes is the safe considered time for ischemic injury. However, this value is been questioned by some researches that considered it a failed algorithm (18, 19). The quantity and quality of remaining renal parenchyma interfere directly in the recovery of renal function; however, in order to confirm this hypothesis, the use of new biomarkers, as well as more sensitive immune histochemical studies are required (20).

According to our study, the presence of lesion in control kidneys in both groups may be justified by crosstalk phenomenon (21). Cross-talk is observed when there is a lesion from a ischemia-perfusion event, that may diffuse to other organs such as lungs, liver and heart. Patho-physiologically, the lesion caused by ischemia-reperfusion promotes activation of pro-inflammatory and pro-apoptotic mediators, and the generation of oxidative stress and production of reactive oxygen species (ROS), that activate leukocytes and modify vasoactive cytokine levels (TNF-α, IL-1β, IL-6, IL-12, IL-15, IL-18, IL-32, and endotelin-1) and chemokines such as the product of leucocyte-endothelium adhesion and leucocyte activation (a characteristic process of ischemic lesion) (22).

The present study had some limitations, such as the reduced number of animals and the dichotomic qualitative statistical analysis that did not englobe all levels of renal lesion (mild, moderate and severe).

The safe time interval depends on several intrinsic and extrinsic variables of the surgery. However, literature shows a great number of studies that analyze differently the ischemic lesion. Until nowadays, there is no available algorithm to predict the risk of acute renal lesion in patients submitted to intra-operative ischemia. Pre-operative evaluation and planning surgical strategy in each case will bring better post-surgical results in relation to renal function maintenance.

CONCLUSIONS

The number of cellular alterations caused by renal ischemia is associated to duration of ischemic injury. It was also verified that there is a significant difference between clamping only the renal artery and that AV group showed lower frequency of lesions than group A (that showed higher number of lesions in lower interval of ischemia time). Minimum time for the occurrence of histological lesions in group A was 10 minutes and for group AV was 20 minutes. The frequency of morphological and structural renal alterations are related to type of clamping and time of ischemia.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared.
REFERENCES


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E-mail: ninagel2003@hotmail.com
Editorial Comment: Study of kidney morphologic and structural changes related to different ischemia times and types of clamping of the renal vascular pedicle

Luciano A. Favorito 1, 2, 3

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Mazzeo and colleagues from Sao Paulo - Brazil shows in a very interesting paper the morphologic and structural changes of renal parenchyma during the clamping of the renal pedicle. Partial nephrectomy (open, laparoscopic or robotic) is considered the gold standard for treating localized renal tumors (1-6). Warm renal ischemia is commonly performed during partial nephrectomy to achieve a bloodless surgical field, however renal ischemia has been associated with renal function impairment (7).

Previous studies shows that the swine is the most adequate model for comparison to human kidney anatomy and physiology (8, 9). Traditionally, 30 minutes is considered the maximum safe time for renal warm ischemia. In a recent study with swine model (10), the renal warm ischemia of 30 minutes by arterial clamping did not caused significant glomerular damage or nephron loss, but if an artery and vein (en bloc) clamping was used, the 30 minutes of warm ischemia caused a decrease in the number of glomeruli.

In the present paper the authors shows that the number of renal parenchymal lesions derived from ischemia is associated with the duration of the insult, but a interesting result was the significant difference between the types of clamping, and the group with clamping of artery and vein (en bloc) clamping used, the 30 minutes of warm ischemia caused a decrease in the number of glomeruli.

According the results of this experimental study during a partial nephrectomy, the en bloc clamping for warm ischemia should be favored over only the renal artery clamping to minimize renal injury after partial nephrectomies, but more studies will be necessary in the future to confirm these results.

REFERENCES


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A prospective study assessing feasibility of performing percutaneous nephrolithotomy in chronic kidney disease patients – What factors affect the outcome?

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1 Department of Urology, King George’s Medical University, Lucknow, India

ABSTRACT

Objectives: To primarily evaluate the functional outcomes of PCNL for bilateral renal calculi/calculi in solitary functioning kidney with Chronic Kidney Disease(CKD). To identify factors affecting the renal replacement therapy following PCNL.

Materials and Methods: Patients with bilateral renal calculi/calculi in solitary kidney and CKD (eGFR<60/s.creatinine>2) and Good Performance Status [Eastern Cooperative Oncology Group (ECOG): 0–2] were included in the study.

Results: A total of 60 patients with CKD who had bilateral renal calculi/calculi in solitary functioning kidney underwent PCNL. At 6 months, eGFR improved or stabilized in 45 (75%) patients, while in 15 (25%) patients eGFR deteriorated. A total of 5 (14.28%) and 2 (25%) patients of CKD stage 4 and 5 respectively had improvement in eGFR as well as CKD stage. Fourteen (82.35%), 21 (60%), 3 (37.5%) patients of CKD stage 3, 4, 5 had improvement in eGFR but not significant enough to cause stage migration. Again 3 (17.65%), 9 (40%) and 3 (37.5%) patients of CKD stage 3, 4, 5 had reduction in eGFR but not significant enough to cause stage migration. None of the patients had worsening of CKD stage. Preoperative CKD stage and eGFR were compared with measurements made at the final follow up visit (6 months).

Conclusion: Our results indicate that most patients of renal calculi with CKD show improvement or stabilization of renal function with aggressive stone removal. Improvement is more in patients who have mild to moderate CKD. Aggressive management of comorbidities, peri-operative UTI and complications may delay or avoid progression of CKD status in such patients.

INTRODUCTION

Chronic kidney disease(CKD) is a common public health disorder that is defined as sustained kidney injury of more than 3 months resulting in a GFR of less than 60 mL/ min/1.73 m² by Kidney Disease Outcomes Quality Initiative (K/DOQI) Advisory Board (1). Current estimates suggest that chronic kidney disease affects 10%-13% of the adult American population (2). In India, it has been recently estimated that the age-adjusted incidence rate of ESRD is 229/million population, and >100,000 new patients enter renal replacement programs annually (3).

Patients with CKD represent 0.8%-17.5% of those presenting with urinary stone disease (4, 5).
The incidence of developing end stage renal disease (ESRD) in patients with renal calculi is 0.2-3.2% (6). The aetiology of renal insufficiency in patients with nephrolithiasis is multifactorial and includes renal obstruction, recurrent urinary tract infections, frequent surgical interventions and coexisting medical disease (4, 5, 7).

Patients with chronic kidney disease frequently have various medical comorbidities, such as diabetes, hypertension, anaemia and bleeding disorders. The likelihood of comorbid conditions may increase the operative risk, the incidence of postoperative complications, and negatively impact the success rate.

Gupta et al. reported that 75.8% of patients with urinary stone disease and deranged renal function requires multiple procedures for stone clearance, including ESWL, PCNL, uretero-renoscopy and open surgical procedures (4).

In the modern era, percutaneous nephrolithotomy (PCNL) has emerged as the gold standard intervention for large burden and complex renal stone disease and is associated with the highest stone free rates (SFRs), usually in a single setting. However, potentially significant complications include bleeding (requiring blood transfusion or embolization), sepsis, pleural and visceral injury. Therefore, the optimal management plan needs to be tailored to individual patient (8).

Many studies have shown the long-term safety of PCNL in patients with normal renal function. However, there are limited data on the outcomes of patients with CKD who undergo PCNL. In this study, we prospectively evaluated the outcomes of renal function in patients with bilateral renal calculi/calculi in solitary functioning kidney with CKD who underwent PCNL, and determined the factors affecting outcome.

AIM AND OBJECTIVES

Primary end point - To evaluate the functional outcomes of PCNL for bilateral renal calculi/calculi in solitary functioning kidney with CKD.

Secondary end point - To identify factors affecting the renal replacement therapy following PCNL in CKD patients.

MATERIALS AND METHODS

Place of Study

This prospective study was conducted at the Department of Urology, King George’s Medical University, Lucknow from October 2015 to October 2017 after Institutional review board clearance. Consent

Written informed consent was taken from all the patients included in this study.

Inclusion Criteria

1. Patients with bilateral renal calculi/calculi in solitary kidney and CKD (eGFR<60/s.creatinine>2)
2. Good Performance Status [Eastern Cooperative Oncology Group (ECOG): 0 – 2]

Exclusion Criteria

1. Poor performance status [Eastern Cooperative Oncology Group (ECOG) >2]
2. Patient not giving consent for PCNL
3. Uncorrected bleeding diathesis
4. Pregnancy

MATERIALS AND METHODS

Initial clinical data including complete blood count, random blood sugar (RBS), serum urea and serum creatinine, electrolytes (sodium, potassium, calcium), prothrombin time (PT and INR), urine routine and culture sensitivity(c/s), X-ray KUB, ultrasound KUB and non-contrast computerized tomography (NCCT) KUB were recorded. Stone complexity was calculated using Guy’s stone score (9). The eGFR for each patient was calculated using a 4-variable MDRD equation (10). CKD was classified using the National Kidney Foundation Kidney Disease Outcome Quality Initiative classification system (11). Pre PCNL serum creatinine and eGFR measurement were done 1 day before the surgery. Performance status was evaluated using Eastern Cooperative Oncology Group (ECOG) Scale (12).

Renal decompression with either Double-J (DJ) stent or percutaneous nephrostomy(PCN) was done for obstructed and infected units.
Post-decompression renal function was assessed serially and patients underwent surgery only after stabilization of eGFR reading recorded at two separate settings.

Antibiotic therapy was given to all patients who had positive urine cultures till documentation of sterile urine. Nephrology consultation was taken regarding optimization of comorbidities and perioperative renal replacement therapy. Appropriate Renal Replacement therapy was given whenever required and as advised by the nephrologist. All PCNL’s were performed at our center by senior consultant urologists or resident trainees under faculty supervision.

**SURGICAL TECHNIQUE**

Following induction of anesthesia, a 5-Fr ureteral catheter (open-ended) was placed to the stone side in lithotomy position via cystoscopy. After returning to prone position, the anatomy of collecting system was delineated using a radiocontrast medium and/or air under fluoroscopy guidance. Puncture and dilatation of the tract was done as per Bull’s eye technique using Amplatz dilators, and procedure performed with a 24-French rigid nephroscope (Richard Wolf, Germany), pneumatic lithotripter (swiss lithoclast®), and grasping forceps. All fragments that were accessible by a rigid nephroscope were removed with a grasping forceps. At the end of procedure, a 20-French nephrostomy tube and 5 French DJ stent were placed in all patients as per our institutional protocol.

Operative time was defined as time elapsed from induction of anesthesia till termination of procedure. Site of puncture (supra vs infra-costal), number of punctures, size of tract, and number of sessions were recorded for each patient.

On postoperative day 1, X-ray KUB and/or USG KUB (for radiolucent calculi) was done in all patients to document stone clearance. The decision of removing the nephrostomy tube was based on nephrostomy tube output, normal intra-operative nephrostogram and normal postoperative X-ray KUB/renal ultrasound (in case of radiolucent calculi). Patients were discharged next morning after removal of per-urethral catheter.

Complete stone clearance was defined as no visible calculi in X ray or NCCT KUB. Clinically insignificant residual fragments were defined as <4 mm. These patients were managed conservatively according to European Association of Urology guidelines (13).

Complications were recorded according to modified Clavien-Dindo classification of postoperative complications (14). In patients with bilateral calculi, PCNL was performed on 2nd side after an interval of 1 month.

All patients were followed up at 2 weeks (for DJ stent removal) and at 6 months when urinalysis, serum creatinine, X-ray KUB and USG KUB, serum creatinine and eGFR were measured. Preoperative CKD stage and eGFR were compared with measurements made at 6 months follow-up visit. Patients were divided into 2 groups by changes in CKD (eGFR) status:

- Group 1- improved or stable disease
- Group 2- worsened disease

The effects of independent variables on kidney function after PCNL, were evaluated by comparing the two groups.

Statistical considerations

The data were entered in an Excel database and analysed with an SPSS version 21.0 (IBM SPSS statistics 21 SPSS Inc.) statistical software package using the Chi-square test, Student’s t-test, and Fischer exact test. P < 0.05 was considered as statistically significant.

**OBSERVATION AND RESULTS**

A total of 60 patients with CKD who had bilateral renal calculi/calculi in solitary functioning kidney underwent PCNL during the period from October 2015 to October 2017. Thirty-one patients had bilateral renal stones while the remaining 29 patients had calculi in solitary functioning kidney (congenital absent kidney-3, history of nephrectomy-2, congenital atrophic kidney-24). Thus, a total of 91 renal units in 60 patients underwent PCNL.

**PREOPERATIVE PARAMETERS**

Demographic parameters

Mean ± SD age was 43.16 ± 16.3 years, the youngest being 12 and the eldest being 75 years of
age. 43 (71.67%) were male and 17(28.33%) were female. 12 (20%) patients had history of previous open surgery while 48 (80%) did not. None had a history of PCNL or ESWL. Fifty two patients had presented with anuria and underwent some form of urinary diversion either with DJ stenting or percutaneous nephrostomy.

Patients were preoperatively classified as having CKD stage 1, 2, 3, 4, 5 respectively according to KDOQI classification. None had stage 1 or 2 CKD while 17, 35 and 8 patients were classified as CKD stage 3, 4 and 5 respectively. Stone complexity was given by Guys stone score and 30, 23, 23, 15 renal units had Guys stone score of 1, 2, 3, 4 respectively.

**OPERATIVE PARAMETERS:**

Operative duration:

Mean ± SD operative time was 120.01 ± 38.24 minutes/renal unit. Operative duration was >100 mins in 62 renal units. A single puncture was used in 44 renal units, while 47 renal units required multiple punctures. Amongst these 25 (27%) renal units required supracostal punctures, while in 66 (73%) kidneys infracostal puncture was achieved.

**COMPLICATIONS**

A total of 46 complications were noted in 20 patients which was summarized according to Clavien Dindo classification. Bleeding necessitating transfusion (26.6%) was the most common complication. Seven (11.6%) patients developed fever that resolved with antipyretics. Ten (16.7%) patients developed UTI necessitating antibiotic therapy. Three (5%) patients developed seizures in immediate postoperative period, that were managed by anticonvulsants. Three (5%) patients developed urosepsis necessitating antibiotics, vasopressors and fluid resuscitation. DJ replacement for prolonged urine leak was required in 4 (6.67%) patients, 3 of whom had urinoma. No mortality was seen in our study. There were no Grade 3b, 4a, 5 complications.

Stone clearance was complete in 49 patients (81.6%) (defined as no residual calculi on NCCT KUB or X-ray KUB) after PCNL.

As an auxiliary treatment, ESWL was done in 2 patients, ureteroscopy in 4, while 5 patients with asymptomatic clinically insignificant residual stones (<4 mm) were followed conservatively. Spontaneous stone passage was seen in 2 patients who were followed conservatively at 3 months.

**FOLLOW UP**

**eGFR value during follow-up**

At 6 months follow up, eGFR improved or stabilized in 45 (75%) patients, while in 15 (25%) patients eGFR deteriorated.

**CKD stage at follow-up**

At 6 months follow up, a total of 5 (14.28%) and 2 (25%) patients of CKD stage 4 and 5 respectively had improvement in eGFR as well as CKD stage. Fourteen (82.35%), 21 (60%), 3 (37.5%) patients of CKD stage 3, 4, 5 had improvement in eGFR but not significant enough to cause stage migration. Again 3 (17.65%), 9 (40%) and 3 (37.5%) patients of CKD stage 3, 4, 5 had reduction in eGFR but not significant enough to cause stage migration. None of the patients had worsening of CKD stage.

These changes are shown in Figure-1. Preoperative CKD stage and eGFR were compared with measurements made at the final follow-up visit (6 months). Patients were divided into 2 groups by changes in CKD stage, including:

- Group 1-improved or stable disease
- Group 2-worsened disease

The effects of independent variables on kidney function after PCNL, including patients age, gender, history of open surgery, comorbid diseases (DM and HTN), stone complexity (GSS), hydronephrosis degree, number of access sites, operative duration, peri-operative complications, stone-free status at postoperative month 6 and recurrent urinary infections during follow up, were evaluated by comparing the 2 groups as shown in Table-1.

On univariate analysis, diabetes, peri-operative complications, patients with history of recurrent UTI and eGFR at follow up were found to be the significant factors affecting outcome.
A multivariable analysis using a logistic regression model was used to determine if any of the potential risk factors was also associated with risk of renal replacement in future. The independent risk factors identified as predictors of RRT were eGFR (coefficient 2.85, \( P = 0.025 \)), degree of hydronephrosis (coefficient 2.10, \( P = 0.04 \)) diabetes (coefficient 1.67, \( P = 0.045 \)) and recurrent UTI (coefficient 2.50, \( P = 0.034 \)).

DISCUSSION

CKD is a major public health problem, and in the surgical setting, not only is it associated with higher risk of anesthetic complications, but also greater risk of post-procedure complications (15). In addition to achieving good stone clearance, surgical interventions employed in the treatment of stone disease must try and preserve maximal renal function. Management of nephrolithiasis in patients with CKD is therefore a difficult challenge for the endourologist as well as nephrologists and calls for careful consideration of the risks against the benefits.

In our study, mean age of patients was 43.16 ± 16.3 years which was slightly lower compared to studies by Kurien et al. (16), Bilen et al. (17), Kumar et al. (18), Akdeniz et al. (19) where the reported mean age of distribution varied from 45–59.5 years. This could be due to larger number of patients of younger age group (<20 years, 6 patients) in our study compared to these studies.

The mean preoperative eGFR was 24.9 ± 8.56 (mL/min/1.73 m²), which was lower than that reported in literature (15–17, 19, 20). This could be due to the inclusion criteria of higher serum creatinine > 2 mg/dL in our study, which was higher than inclusion criteria (eGFR <60/Serum creatinine >1.5) taken in these studies.

Seven (11.6%) patients had diabetes. This was comparable to the incidence of DM in studies reported by Akdeniz et al. (19), Akman et al. (15), Sairam et al. (21) and 12 (20%) patients had hypertension. There has been large variation in the reported incidence (8.6–42%) of hypertension in other studies (15, 17, 19). Jones et al. (8) in a systemic review of 9 studies (n=1851), reported...
Table 1 - Univariate analysis of patient and procedure related factors affecting kidney function after PCNL.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n)</th>
<th>Group 2 (n)</th>
<th>P value</th>
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<td>39</td>
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<tr>
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<td>6</td>
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<tr>
<td>Complications</td>
<td></td>
<td></td>
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<tr>
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<td>11</td>
<td>9</td>
<td></td>
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<tr>
<td>No</td>
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<td>Recurrent UTI</td>
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</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42</td>
<td>11</td>
<td></td>
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</table>
30.7% incidence rate of hypertension which was comparable to our study.

The mean operative time was 120.01 ± 38.24 (range 60-250) minutes, which was higher than those reported in literature (15, 18, 19). This could be due to trainees performing some of the procedures, leading to longer operative time or due to more complex stones (43% GSS 3 or 4). None of other studies reported stone burden in form of GSS but mean stone size in these studies was 706.8 mm² (range 357-1484 mm²).

Single access was gained in 48.3% of cases with a mean of 1.57 punctures/renal unit. This was lower compared to various studies that report frequency of single access to be 68–80%. This could be due to the high frequency of complex calculi (GSS 3-4, 41.7%) which required multiple access to achieve maximal stone clearance. Complete stone clearance was achieved in 81.6% cases which is also in concordance with that reported in literature (70-90%) (15-19).

Complications

Seven (11.6%) patients developed fever (grade 1) which was managed successfully by conservative management. Blood transfusion due to postoperative drop in haemoglobin was the most common complication seen in 16 (26.6%) patients. This was similar to the reported incidence of blood transfusion in various studies from 9.6-36% (16-19). Such high rates of blood transfusion could be attributed to pre-existing anemia and platelet dysfunction in CKD patients. None of the patients reported with delayed haemorrhage or required angioembolization.

Seizures were seen in 3 patients in immediate postoperative period which was managed successfully by anti-convulsants. Seizures could be attributed to altered anaesthetic drug metabolism or electrolyte imbalance seen in CKD patients.

DJ stent was routinely done in all our patients. However, 9 patients developed urinary leakage following nephrostomy removal. In five patients it subsided by conservative management like anticholinergics and compression dressing. In 4 patients who did not respond to conservative management, DJ stent replacement was done following which it resolved. Akman et al. (15) in his series of 177 patients reported 2.2% incidence of DJ stenting for prolonged urine leak. Ansari et al. (22) in their study of 576 patients, found stone complexity, grade of hydronephrosis, renal parenchymal thickness in access line, intra-parenchymal renal pelvis, multiple punctures, surgeon’s experience, and residual stones as factors for prolonged urinary leakage post-PCNL. Possible explanation of this high incidence (6.6%) of prolonged urine leak in our study could be multiple punctures (2 patients), gross hydronephrosis (1 patient) and presence of CKD which is associated with delayed wound healing.

Urosepsis (Grade 4b) occurred in 3 (5%) patients, which was similar to incidence reported in literature of 2.8-9.9% (15-17). Such high incidence of sepsis could be due to immune-deficiency in CKD patients, staghorn calculi, presence of DJ stent/PCN in patients. All of these patients were managed aggressively in ICU setting with antibiotics, fluid resuscitation, vasopressors. No mortality was seen.

FOLLOW-UP RENAL FUNCTION

Mean eGFR during the preoperative period, and at 6 months follow-up was 24.9 ± 8.56 and 27 ± 10.13 mL per minute/1.73 m² respectively. Overall renal function improvement was seen in 45 (75%) patients, while in 15 (25%) patients it deteriorated. This was in concordance with overall improvement in renal function seen in reported literature (15-19). Fourteen (82.3%), 26 (64.28%) and 5 (62.5%) patients in stage 3, 4, 5 showed improvement in eGFR post intervention respectively. Kurien et al. in their study suggested that an improvement in eGFR was greater in patients with mild to moderate renal failure than in those with severe CKD (16). It would be reasonable to assume that those patients with severe renal failure would be less likely to gain benefit, principally because the damage already done to the kidney was severe and irreversible.

However, in a study done by Bilen et al., patients with late stage CKD, although a small number, achieved significant improvement, while
unexpected deterioration was seen in some patients with less severe CKD (17).

Urinary tract infection appeared to be the underlying cause of the observation in the latter study, emphasizing the need for constant vigilance against infection in all PCNL cases regardless of CKD status. However studies agreed that through ever more aggressive stone removal and more effective prevention of infection, renal replacement therapy can still be deferred in most patients with renal stone disease (16, 17).

The results of other studies are summed up in Table-2.

On univariate analysis, diabetes (p=0.03), perioperative complications (p=0.01) and recurrent UTI (p=0.03) were found to be significant factors that negatively impact the outcome.

Akman et al. (15) in their study of long-term outcomes of percutaneous nephrolithotomy in 177 patients with chronic kidney disease, found that diabetes and preoperative or postoperative complications predicted renal function on multivariate regression analysis. Kurien et al. (16) in their study of 91 patients found postoperative complications and peak eGFR (less than 30 mL/minute/1.73 m²) at follow-up to predict renal deterioration and need for renal replacement therapy (RRT). Renal parenchymal thickness (<8 mm) also predicted the need for RRT.

Bilen et al. (17) in their study found that only the presence of urinary-tract infections had a tendency to negatively affect the GFR.

Ozden et al. (20) reported that diabetes mellitus (odds ratio 15.82, P=0.036) and urinary infection (odds ratio 10.6, P=0.04) were predictive

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Mean (SD, range) years</th>
<th>Diabetes</th>
<th>Inclusion criteria (eGFR (mL/min/1.73 m²))</th>
<th>Mean Pre-Op. eGFR (mL/min/1.73 m²)</th>
<th>Mean Operative time Min. (SD,range)</th>
<th>Complication requiring Haemorrhage Transfusion, Sepsis</th>
<th>Follow up eGFR (mL/min/1.73 m²)</th>
<th>Overall change</th>
</tr>
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<tr>
<td>Present study</td>
<td>43.16 (16.38, 12-75)</td>
<td>11.6%</td>
<td>&lt;60/S. Creatinine &gt;2</td>
<td>24.9 ± 8.56</td>
<td>120.01 (38.24, 60-250)</td>
<td>26.6% 5% 27</td>
<td>27</td>
<td>Improved</td>
</tr>
<tr>
<td>Bilen et al. (17)</td>
<td>53.2 (NR, 20-81)</td>
<td>1.62%</td>
<td>&lt;60</td>
<td>S. Creatinine 1.87</td>
<td>101.4 (NR, NR)</td>
<td>36% 3% 48.4</td>
<td>48.4</td>
<td>Improved</td>
</tr>
<tr>
<td>Kurien et al. (16)</td>
<td>52.5 (13, NR)</td>
<td>-</td>
<td>S. Creatinine &gt;1.5</td>
<td>S. Creatinine 3.2</td>
<td>NR</td>
<td>20.5% 9.9% 43.3</td>
<td>43.3</td>
<td>Improved</td>
</tr>
<tr>
<td>Akman et al. (15)</td>
<td>54.3 ± 12.1 years</td>
<td>19.8%</td>
<td>&lt;60</td>
<td>4.8</td>
<td>65.12 (22.83, NR)</td>
<td>9.6% 2.8% 48</td>
<td>48</td>
<td>Improved</td>
</tr>
<tr>
<td>Ozden et al. (20)</td>
<td>-</td>
<td>-</td>
<td>&lt;60</td>
<td>39.9</td>
<td>NR</td>
<td>- - 51.3</td>
<td>51.3</td>
<td>Improved</td>
</tr>
<tr>
<td>Akdeniz et al. (19)</td>
<td>59.5 (7.85, 39-78)</td>
<td>11.8%</td>
<td>&lt;60</td>
<td>4.8</td>
<td>NR</td>
<td>11.8% NR 51.8</td>
<td>51.8</td>
<td>Improved</td>
</tr>
<tr>
<td>Sairam et al. (21)</td>
<td>-</td>
<td>18.8%</td>
<td>-</td>
<td>NR</td>
<td>89 (52.3, NR)</td>
<td>- - -</td>
<td>-</td>
<td>Improved</td>
</tr>
<tr>
<td>Kumar et al. (18)</td>
<td>45 (NR, 18-65)</td>
<td>-</td>
<td>s.creat. &gt;4.5</td>
<td>s.creat. -6.3</td>
<td>110</td>
<td>20% 20% 2.56 (s.creatinine)</td>
<td>Improved</td>
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</table>
of renal function deterioration at 1 year on multivariate analysis.

Our results indicate that most patients of renal calculi with CKD show improvement or stabilization of renal function with aggressive stone removal. Improvement is more frequent in patients who have mild to moderate CKD. Although complications are higher in CKD patients most are of low grade, thereby confirming the safety and efficacy of PCNL in CKD patients. Aggressive management of comorbidities and perioperative UTI and complications in these patients may delay or avoid progression of CKD status in these patients.

LIMITATIONS OF OUR STUDY

Our study comprised of only 60 patients with limited follow-up period of 6 months. More insight can be achieved on the renal function status with a longer follow-up. The other limitation is the lack of metabolic evaluation and stone analysis in our study. Recent studies highlighted the impact of aggressive medical treatment together with metabolic evaluation on post-PCNL stone recurrence and residual stone regrowth (23).

CONCLUSION

PCNL can be carried out with acceptable complication rates in patients with CKD. Diabetes, peri-operative complications in form of bleeding and recurrent UTI's are significantly associated with deterioration of renal function. Post-operative complications are significantly associated with negative outcomes and hence one should be cautious to prevent them or manage them aggressively for a successful outcome.

CONFLICT OF INTEREST

None declared.

REFERENCES


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E-mail: rebellite@gmail.com
Correlation of tools for objective evaluation of infravesical obstruction of men with lower urinary tract symptoms

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1 Universidade Estadual de Campinas - Unicamp, Campinas, SP, Brasil

ABSTRACT

Purpose: To identify how the most frequently used parameters in daily clinical practice diagnosing bladder outlet obstruction (BOO) due to benign prostate hyperplasia (BPH) correlate to each other.

Materials and methods: The study included 452 patients with lower urinary tract symptoms (LUTS) of the UNICAMP urology outpatient clinic of LUTS. Inclusion criteria: patients with BOO due to BPH who agreed to participate in the study. Exclusion criteria: patients with urinary tract infection, neurological diseases that compromised the lower urinary tract, prior prostatic surgery, radiotherapy or urethral stenosis. Patient assessment: history, international prostate symptoms score (IPSS), nocturnal quality of life score (NQoL) questionnaires, physical and digital rectal examination (DRE), PSA, transabdominal ultrasound with intravesical prostate protrusion (IPP), post-mictional residue and free uroflowmetry.

Results: There was no strong Spearman correlation among the studied variables. The only moderate correlations occurred between IPSS and NQoL (p <0.001; c=0.56) and between IPP and prostate volume (p <0.001; c=-0.57). Weak correlations between IPP and post-mictional residue (p <0.001; c=-0.31) and free uroflowmetry (p <0.001; c=-0.26); and between IPSS and free uroflowmetry (p <0.001, c=0.21) were observed.

Conclusion: In this study, we found moderate, weak, very weak and absent correlation among the various parameters used in the diagnosis and management of BOO due to BPH. As the value of these tools is variable, the creation of a logical and objective algorithm was not possible and the treatment is based on the interpretation of clinical symptoms.

INTRODUCTION

Lower urinary tract symptoms (LUTS) are frequent in adult males, with an incidence approximately of 40% of those with more than 65 years old. They are consequent of prostate and bladder micturition disorders and include storage symptoms (urgency, frequency, nocturia and incontinence), emptying symptoms (weak stream, urinary exertion, hesitancy and terminal dripping) and post-micturition symptoms (incomplete emptying, post-micturition dripping) (1, 2).

Evaluation of patients with LUTS includes anamnesis, validated questionnaires, physical exam (particularly digital rectal examination-DRE), and auxiliary tests (urine, PSA, ultrasound).

Among all validated questionnaires, the most used is the International Prostatic Symptoms Score (IPSS), that includes eight questions, seven related to symptoms and one related to quality of
life (IPSS-QoL). It rates the symptoms as mild (0-7 points), moderate (8-19 points) and severe (20-35 points), and it is an important tool to characterize the severity of symptoms and the follow-up of patients (3).

PSA values above 1.5ng/mL may be related to prostates >30g, with positive predictive value of 78%, and positively correlates to the risk of progression of LUTS (4).

The effect of nocturia on quality of sleep and life may be evaluated by the “Specific Questionnaire of Nocturia and Quality of Life” (NQoL), that includes three domains: sleep/energy (7 questions, scale 0-28), bothersome/worry (5 questions, 0-20 points), and a global question about quality of life (0-4), totaling 13 items; the question form is self-administered, takes 5 minutes to conclude, and proved to be consistent and reproducible (5), although not much used in clinical practice.

While severe LUTS are correlated to prostate anatomy, particularly intravesical protrusion of prostate (IPP), lower quality of life and predispose to inguinal hemaia (6, 7), mild LUTS do not linearly correlate with the intensity of symptoms and bladder outlet obstruction; also, progressive benign prostatic hyperplasia causes bladder dysfunction that interferes with the intensity of LUTS, regardless the degree of bladder outlet obstruction (8-11).

Strope et al. showed that in the USA, despite the availability of guidelines proposed by the American Urological Society to treat benign prostatic hyperplasia (BPH), it is observed a great diversity of use and precision of available tools (12).

**OBJECTIVE**

To correlate the most frequent parameters used in daily clinical practice to diagnose and treat bladder outlet obstruction (BOO) due to BPH.

**MATERIALS AND METHODS**

The study included 452 patients that signed a free informed consent CAAE 84939917.6.0000.5404, during the first interview. All patients attended the ambulatory of Urology of UNICAMP from May, 2018 to September, 2018, complaining of LUTS.

Inclusion criteria: Patients with LUTS that agreed to participate in the study after signing the free informed consent.

Exclusion criteria: Patients with prostate cancer, urinary infection, neurological diseases that affected the urinary system, previous prostatic surgery, radiotherapy or urethral stenosis.

Patient evaluation: Patients were evaluated by history, International Prostatic Symptom Score (IPSS), Nocturnal Quality of Life Score (NQoL), general physical exam and systematized rectal examination (13), serum PSA, transabdominal prostate ultrasound evaluating intravesical prostatic protrusion (IPP), prostatic volume and post-micturition residue, and free uroflowmetry (Qmax) determined by one of the authors (OM). Patients were evaluated before the introduction of drugs in order to avoid bias.

**Statistical analysis**

Data were analysed (medium, standard deviation, minimum, maximum, median) and multiple regression models and Spearman Test with Bootstrap method were used to correlate multiple variables among themselves: age, IPSS, IPSS-QoL, NQoL, Qmax, IPP, prostate volume, post-micturition residue and PSA. Significance level was p\(\leq 0.05\) and correlation coefficient (c) was classified as very weak (0.00-0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79) and very strong (0.80-1.00).

**RESULTS**

Demographic data of this cohort are summarized at Table-1.

Significant correlations included:

1. Moderate:
   a) IPP with prostate volume (p<0.0001; c=0.57), Figure-1;
   b) IPSS and NQoL (p<0.0001; c=0.56), Figure-2.

2. Weak:
   a) IPP and post-micturition residue (p <0.0001; c=0.31) and Qmax (p <0.0001; c=0.26);
   b) IPSS and Qmax (p <0.0001, c=-0.21).
3. Very weak:
   a) Age and IPP (p=0.003; c=0.14), Qmax (p=0.0003, c=-0.17) and IPSS-QoL (p=0.002, c=-0.14);
   b) IPSS and post-micturition residue (p=0.0006; c=0.16) and PSA (p=0.04, c=0.14);
   c) Prostate weight and age (p <0.0001, c=0.18).

**DISCUSSION**

Since there are no measures to evaluate reliable clinical symptoms or specific and sensitive

<table>
<thead>
<tr>
<th>Table 1 - Characteristics of the studied group.</th>
<th>Number of observations</th>
<th>Medium±SD</th>
<th>Minimum/Maximum</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>452</td>
<td>65.8±9.2</td>
<td>30/90</td>
</tr>
<tr>
<td>NQoL (Nocturnal quality of life)</td>
<td>452</td>
<td>19±10.3</td>
<td>0/52</td>
</tr>
<tr>
<td>IPSS (International prostatic symptoms score)</td>
<td>452</td>
<td>16.2±8.53</td>
<td>0/35</td>
</tr>
<tr>
<td>Qol (Quality of life)</td>
<td>452</td>
<td>3.02±1.49</td>
<td>1/6</td>
</tr>
<tr>
<td>Qmax (maximum flow)</td>
<td>452</td>
<td>10.4±4.8</td>
<td>1/39</td>
</tr>
<tr>
<td>Urinated volume</td>
<td>452</td>
<td>155±45.7</td>
<td>16/480</td>
</tr>
<tr>
<td>Prostate weight (g)</td>
<td>452</td>
<td>40.9±24.4</td>
<td>7/179</td>
</tr>
<tr>
<td>Post-micturition residue (mL)</td>
<td>452</td>
<td>74.3±87.4</td>
<td>0/630</td>
</tr>
<tr>
<td>Intravesical protusion of prostate (mm)</td>
<td>452</td>
<td>5.6±5.8</td>
<td>0/33</td>
</tr>
</tbody>
</table>

**Figure 1 - Spearman significant correlations for IPP.**

<table>
<thead>
<tr>
<th>Residual urine</th>
<th>Flow</th>
<th>Prostate weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPP</td>
<td>0.31034</td>
<td>-0.26027</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Scatter Plot Matrix**
exams to evaluate the severity of bladder outlet obstruction (14), it is necessary to understand a series of correlated events and their potential pathophysiological disturbances.

There is no accepted universal “standardization” to diagnose and treat prostatic benign hyperplasia (BPH) with bladder outlet obstruction (BOO). Age, bladder perfusion, innervation and interactions of urothelium are responsible for LUTS and not only BOO (15-18).

Since clinical symptoms do not correlate with the grade of obstruction, at present, only urodynamic evaluation is the only objective method to diagnose BOO, and it is considered the gold standard method (17-21). However, urodynamics is an invasive method, expensive, that needs equipment not always available in different centers, and its routine use is improbable (20-23).

Physiologically, micturition is a complex phenomenon that depends on the interaction of several factors such as: afferent sensitive component, central nervous system (CNS), that coordinate these stimuli, muscle contraction and afferent component, including neurotransmitters; these components are not individualized but work together, and the weight of each one on micturition is variable; all these factors are responsible for the symptoms, and even men with obstruction may be asymptomatic (24).

BOO may present different heterogeneous signs and symptoms; clinical history is inaccurate for early diagnosis, and also, detrusor hypocontractility may be a differential diagnosis or also be present, since its clinical presentation is similar, with different pathophysiology and completely different treatment (25).

The most used tools to diagnose BPH and BOO include: complete medical history, IPSS and NQoL questionnaires, general physical exam and digital rectal examination, PSA, transabdominal prostatic ultrasound and free uroflowmetry.

In this study, IPSS did not correlate with age or prostate weight, but there was a weak negative correlation with maximum flow, and positive very weak with residual urine and PSA, since their characteristics are not exclusively related to BOO as shown in literature (26).

In order to improve the evaluation of quality of life it is possible to use other parameters such as productivity, sleep and vitality. In this matter, NQoL is a question form that does not quantify obstruction (the same as IPSS), but complements

<table>
<thead>
<tr>
<th>Residual urine</th>
<th>Flow</th>
<th>NQoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS</td>
<td>0.11428</td>
<td>-0.21033</td>
</tr>
<tr>
<td>0.0151</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</table>
clinical evaluation of its impact on quality of life. In this study, IPSS and NQoL correlated moderately (p <0.0001; c=0.56), and the results were very similar to those of a Japanese study (p <0.0001; c=0.58) (27).

With ultrasound, it was observed a moderate correlation of IPP and prostate weight, and weak of IPP and residual urine and maximum flow, meaning that the higher the prostate volume, the higher the chance of IPP, in agreement with a previous study (6).

The study of free uroflowmetry is recommended due to its non-invasive nature, and it is used to screen and investigate BOO for a long time; however, although identifies patients with normal or low flow, it is not specific and does not differentiate low flow due to obstruction or hypococontractility.

Urinary flow results of a contraction of detrusor muscle against urethral resistance, and the loss of energy due to friction is 70% in men and 50% in women; therefore, low flow may be caused by lower contraction of detrusor muscle or higher urethral resistance, and maximum flow analysis may be inaccurate to diagnose BOO (23).

BOO due to BPH is related to many more characteristics than mechanical obstruction, due to alterations of detrusor muscle, perfusion, expression of neurotransmitters at urothelium, that contribute to symptoms. This is the new concept of LUTS due to BOO secondary to BPH, related to many more hypothesis for understanding its pathophysiology (15, 17, 28).

A Chinese study corroborated our result, it described an evident overlapping of parameters used to evaluate LUTS. Despite significant correlations, it is not possible to predict the intensity of symptoms of obstruction, using isolated tools (29). Also, a Danish study observed statistically significant but weak correlations among non-invasive objective parameters during evaluation of LUTS (30).

Taken all together, these data support a complex correlation among the studied parameters, however IPSS shows a good correlation with patient’s perception of his quality of life, a main aspect to define and propose treatment and response evaluation in clinical trials (26).

Prospective evaluation with validated different and correlated tools in the same group of patients with LUTS, attended in a systemized manner in urological ambulatories, is important as demonstrated in the present study, that has also some limitations. This is a series of LUTS patients and the results can not be extrapolated to different scenarios, and not all patients had PSA values available.

Although the impact of nocturia on quality of sleep and life was evaluated, in urological researches this is an aspect not much studied. Our study is the second to correlate IPSS and NQoL (27).

Future studies are needed to confirm and broaden the current results and should include urodynamics studies, although invasive when compared to the used tools, in order to evaluate in detail bladder function, and to classify patients with hyperactive bladder, urinary incontinence and with obstruction.

CONCLUSIONS

In this study, we have found moderate, weak and very weak correlations among several parameters used to diagnose LUTS with BOO due to BPH. Since the value of these parameters is variable, particularly when the symptoms are mild, the creation of a logic and objective algorithm in the beginning and monitoring of treatment was not possible, and at present it is still based on interpretation of clinical symptoms.

CONFLICT OF INTEREST

None declared.

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Efficacy and tolerability of mirabegron in female patients with overactive bladder symptoms after surgical treatment for stress urinary incontinence

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ABSTRACT

Purpose: To evaluate the efficacy and tolerability of mirabegron in females with overactive bladder (OAB) symptoms after surgical treatment for stress urinary incontinence (SUI).

Materials and Methods: The study was conducted with a prospective, randomized and double-blinded design. 62 patients over the age of 40 who met the inclusion-exclusion criterias of the study were enrolled and randomly divided into two groups as Group A (mirabegron 50mg) and B (solifenacin 5mg). Patients were compared based on efficacy of treatment [Patient Perception of Bladder Condition (PPBC) scale and micturition diaries], safety of treatment (heart rate, systolic and diastolic blood pressure, adverse events), number of micturitions per day, patient’s satisfaction status after treatment [Visual Analog Scale(VAS)] and quality of life.

Results: The mean age of the population was 48.2±3.8 years and the duration of OAB symptoms was 5.9±2.9 months. Baseline values for the mean number of micturitions, volume voided in each micturition, nocturia episodes, urgency and urgency incontinence episodes were 15.3±0.34, 128±3.88mL, 3.96±1.67, 5.72±1.35 and 4.22±0.69, respectively. After treatment, values for these parameters were 11.7±0.29, 164.7±2.9mL, 2.25±0.6, 3.38±0.71, 2.31±0.49 respectively. Quality of life score, symptom bother score, VAS for treatment satisfaction score, PPBC score after treatment were 66.1±0.85, 43.7±0.77, 4.78±0.14, 4.78±0.14, respectively. There were no significant differences between two groups on any parameter. However, mirabegron showed better tolerability than solifenacin, particularly after 6 months.

Conclusion: Mirabegron is safe, effective and tolerable in the long-term treatment of females with OAB symptoms after surgery for stress urinary incontinence.

INTRODUCTION

Urinary incontinence is a bothersome symptom that has a serious impact on quality of life (1). It is classified into three types as stress urinary incontinence, urgency incontinence and mixed type incontinence due to the different pathophysiological mechanisms underlying (2).

Stress urinary incontinence (SUI) is caused by the impairment of pelvic and vaginal support to the urethra due to aging and decreasing estrogen levels in the perimenopausal period (2). If pelvic
floor training which contributes to the support of the female urethra fails, surgical treatment for SUI is considered (3).

Overactive bladder is a symptom complex defined by urinary urgency, with or without urgency urinary incontinence (UUI), usually accompanied by frequency and nocturia in the absence of any obvious pathology. UUI is characterized by overactive bladder (OAB) symptoms mentioned above and additionally urinary incontinence (2). It may be seen purely, without SUI, or with SUI that is classified as mixed urinary incontinence. Patients undergoing surgical treatment for SUI may experience aggravation of OAB symptoms or develop de novo UUI after the intervention (3).

Oral anti-muscarinic agents have played the main role in the treatment of UUI for several decades (4). Although UUI frequently requires long-term treatment, inadequate response and significant adverse effects of anti-muscarinics have limited their long-term use (4), also led to frequent changes in treatment schedules.

Mirabegron is a relatively new drug, an oral β3 adrenoreceptor agonist which facilitates urine storage by relaxing detrusor muscle (5). This different mechanism of action provides mirabegron comparable efficacy to anti-muscarinics, also less side effects than them such as dry mouth, constipation, blurred vision or cognitive impairment (4). Acceptable safety and tolerability of mirabegron leads to less discontinuation by patients in long-term treatment.

After SUI surgery, OAB symptoms constitute a major problem for patients who are in hopes of being cured. Stanford et. al. (6) reviewed the complications of suburethral sling procedures, including 20 studies with a total of 1950 patients. They found an overall incidence of de novo OAB symptoms of 15.4%, ranged from 1.7% to 42% (6). The first step in the management of OAB symptoms after SUI surgery is to rule out urinary tract infection, bladder outlet obstruction, mesh erosion, foreign body in the urethra or bladder. Then, OAB symptoms can be managed as primary OAB (treated by an antimuscarinic or a β3 adrenoreceptor agonist).

Besides, this article aims to discuss whether efficacy and tolerability of mirabegron is adequate and acceptable in female patients with OAB symptoms after surgical treatment for SUI.

**MATERIALS AND METHODS**

The study was designed as a prospective, randomized and double blinded study and conducted in accordance with ethical principles derived from The Declaration of Helsinki and Good Clinical Practice. Ethical approval was obtained from the local ethical committee. In addition, a written informed consent was taken from all patients participated.

Female patients who had a history of surgery for SUI and older than the age of 40 were prospectively enrolled to the study. Patients were randomized into two groups (Groups A and B). Block design was used for randomization. Mirabegron (oral, 50mg once a day) was given to patients (n=35) in Group A whereas solifenacin (oral, 5mg once a day) was given to patients (n=36) in Group B at the first visit. Follow-up visits were performed in every 3 months till 12th month.

Primary endpoints of our study were evaluation of the efficacy and safety. Efficacy and safety were both evaluated by a single urologist in each outpatient visit. In addition, number of micturitions per 24h was accepted as a primary endpoint. All data were collected at the last visit (12th month). Patients who lost to follow-up were excluded from the study.

Patient Perception of Bladder Condition (PPBC) scale and micturition diaries were used for the evaluation of efficacy. PPBC is a six-point scale on which patients are asked to rate their perceived bladder condition, ranging from 1 “no problems at all” to 6 “many severe problems”. Number of micturitions, voided volume in each micturition, nocturia episodes, urgency episodes and urgency incontinence episodes were recorded in 3-day micturition diary. In addition, a Visual Analog Scale (VAS) ranging from 0 to 10 was used for the evaluation of patient’s satisfaction after treatment. Moreover, Health Related Quality of Life (HRQoL) and symptom bother score were performed to assess the improvement in quality of life.

Safety was assessed by evaluating vital signs as fever, heart rate (n/min) and blood pressure; by performing electrocardiogram (ECG) and...
laboratory tests (urinalysis, complete blood count, electrolytes, renal and hepatic function tests). During follow-up, all adverse events were recorded. Expected side effects of mirabegron or antimuscarinics such as cardiac arrhythmias, hypertension, nasopharyngitis, dry mouth, constipation were reported in details in each visit. Indication for the treatment cessation is accepted as any life-threatening event or significant decrease in patient satisfaction assessed by Health Related Quality of Life (HRQoL) questionnaire. A hypertensive event was considered as any measurement of systolic blood pressure ≥140mm Hg or any measurement of diastolic blood pressure ≥90mm Hg, additionally an increase of ≥20mm Hg in systolic blood pressure or an increase of ≥10mm Hg in diastolic blood pressure.

Prior use of antimuscarinics or any other treatments for urinary incontinence were recorded in the first visit. Because, it was mandatory to stop using all anti-incontinence treatments before the beginning of the study, those who used antimuscarinics at the last 3 months were excluded from the study. Additionally, patients who had any perioperative complication (permanent urinary retention, mesh erosion, bladder perforation or adjacent organ injury) during SUI surgery were excluded. Other drugs used for different co-morbidities such as diabetes mellitus, hypertension or any other chronic disease were permitted to be used during the study, but recorded carefully for close follow-up in case of any adverse events.

Statistical analysis

For analysis, SPSS 22.0 (IBM Company, Chicago) was used (7). Changes in all parameters of efficacy and safety from the first visit to the final visit for both groups were analyzed by using analysis of covariance model (ANCOVA) to obtain adjusted means. For statistical significance, p-value of <0.05 was accepted.

RESULTS

Table-1 provides an overview of the baseline characteristics of the study population. A total of 71 patients participated in the study; however, 9 were excluded due to lacking any of the visits (5 in Group-A, 4 in Group-B). The data of remaining 62 patients were evaluated. The mean age of the population was 48.2±3.8 years and similar in both groups (Table-1). Vast majority of the participants were treatment-naive patients, only 33% had a history of prior use of any drug for OAB symptoms. Patients with MUI constituted majority of the participants in the study, as only 9 patients reported de novo OAB symptoms. Mean duration of OAB symptoms was 5.9±2.9 months. The mean duration time between SUI surgery and enrollment in the study protocol was 26 months. Transobturator tape (TOT) and Tension-free vaginal tape (TVT) procedures were performed for SUI surgery in 48 and 14 patients, respectively. Three patients in TOT and 1 patient in TVT group described insignificant residual SUI that required lower than 2 pads daily.

Efficacy assessments are summarized in Table-2. Several parameters were assessed to compare the efficacy of both drugs for the treatment of OAB symptoms in women after surgery for SUI. There was no statistically significant difference between the baseline values of two groups in any parameter. In post-treatment results, Group-A showed similar results with Group-B in all parameters (Table-2). Mirabegron group provided even slightly better results for number of micturitions per 24h though the difference was not statistically significant (p: 0.37).

Patient reported outcomes (PPBC and TS-VAS) all revealed that the efficacy of mirabegron was comparable to that of solifenacin. In addition, quality of life which was assessed by the responder analyses, was similar and better than the beginning in both groups.

Safety assessments are provided in Table-3 in details. Possible side effects, adverse events or any factor leading discontinuation of treatment were reported. Hypertensive events were more frequent in Group-B. A total of 12 events in 8 different patients were recorded (Table-3). All of the hypertensive events were temporary so did not require to stop the treatment. Sinus tachycardia was observed in 2 patients of Group-A. It was asymptomatic, only recorded in ECG and did not persist in the follow-up visits. QT interval prolongation was not recognized in any patients participated.
Nephrotoxicity and hepatotoxicity was assessed by monitoring serum creatinine levels and liver enzymes in each visit performed. Insignificant and temporary changes as slightly elevated serum alanine transaminase levels in 2 patients and creatinine levels in 3 patients, were observed but did not require to stop the treatment. No cognitive impairment was recognized in any participants of the study. Acute urinary retention (AUR) was observed in only one patient of Group-B but did not persist despite continuation of the treatment. Urinary tract infection (UTI) rates were similar in both groups. UTIs were not severe that oral antibiotics therapy was adequate in all cases. A total of 17 patients stopped the treatment before the end of the study. In all cases, certain side effects were responsible for discontinuation rather than inadequate response. Mean duration of treatment was 10.8 months in total but significantly longer in the mirabegron group (11.4 vs. 10.3, p:0.042) Vast majority of patients quitted participated in the solifenacin group (13 of 17, 76%) and dry mouth was the primary factor leading to the discontinuation of treatment (11 of 13 patients in Group B). Four patients discontinued mirabegron due to the side effects, particularly headache and nasopharyngitis. But in general mirabegron provided higher tolerability than solifenacin.

**DISCUSSION**

Urinary incontinence has always been under debate in Urology (8). Several choices of treatment, indispensable side effects in each option and challenging clinical cases make urinary incontinence a certain point of interest for most urologists (8).

One of the most troublesome aspects of treatments for urinary incontinence is low patient
satisfaction rates (9). Probably there are so many reasons for unsatisfaction of the patients but serious side effects might be the leading problem for patients to overcome in the long-term treatment of urinary incontinence.

This study aims to determine whether mirabegron is safe and effective in females who has a history of surgical intervention for SUI by comparing with solifenacin which is a widely accepted anti-muscarinic in the treatment of OAB symptoms. There are several studies in the literature that shows the efficacy of mirabegron but most of them focus on pure UUI or mixed urinary incontinence with a predominantly component of OAB symptoms. Our study focuses on a different population. After a surgical intervention for SUI, either de novo or persisting and aggravating OAB symptoms lower the satisfaction rate of patients if it is not managed properly. This clinical condition would be considered as a different situation from primary OAB due to its different etiology.

Urodynamic studies show that detrusor overactivity occur in these patients (10). The reason why detrusor activity is observed in these patients is yet to be revealed but a possible mechanism is the adaptation of detrusor muscle to the new circumstances occurred in the lower urinary tract. In other words, it may be regarded as a response by detrusor to the increased urethral resistance provided by SUI surgery. Frequently patients suffering from OAB symptoms apply to their physician after a few weeks following surgery. Probably this period of time is required for gaining detrusor overactivity particularly in de novo OAB patients.

Long-term treatment would be required in these patients to overcome OAB symptoms. Therefore, mirabegron seems to be a good option in these cases with its well tolerability.

Several anti-muscarinics have been used in the treatment of de novo or preexisting and persisting OAB symptoms after surgery for SUI since their efficacy was proven for the treatment of UUI. Among other anti-muscarinics, solifenacin would be a sensible option with its once a day usage to compare with mirabegron, in this way we tried to avoid a possible bias due to the multiple usage of another anti-muscarinic, because of its short half-life time. But the main reason of choosing solifenacin 5mg for comparison with mirabegron is its widely availability in Turkey. Some

### Table 2 - Parameters for Efficacy Assessment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Group A</th>
<th>Group B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of micturitions during 3-day micturition diary, Mean±SD</td>
<td>11.73±0.29</td>
<td>11.62±0.27</td>
<td>11.81±0.32</td>
<td>0.37</td>
</tr>
<tr>
<td>Volume voided in each micturition during 3-day micturition diary (mL), Mean±SD</td>
<td>164.71±2.96</td>
<td>165.73±2.94</td>
<td>163.69±2.98</td>
<td>0.19</td>
</tr>
<tr>
<td>Nocturia episodes during 3-day micturition diary, Mean±SD</td>
<td>2.25±0.61</td>
<td>2.20±0.57</td>
<td>2.30±0.64</td>
<td>0.41</td>
</tr>
<tr>
<td>Urgency episodes during 3-day micturition diary, Mean±SD</td>
<td>3.38±0.71</td>
<td>3.15±0.73</td>
<td>3.62±0.68</td>
<td>0.29</td>
</tr>
<tr>
<td>Urgency incontinence episodes during 3-day micturition diary, Mean±SD</td>
<td>2.31±0.49</td>
<td>2.27±0.47</td>
<td>2.36±0.51</td>
<td>0.42</td>
</tr>
<tr>
<td>HRQoL Score, Mean±SD</td>
<td>66.1±0.85</td>
<td>65.8±0.82</td>
<td>66.2±0.87</td>
<td>0.30</td>
</tr>
<tr>
<td>Symptom Bother Score, Mean±SD</td>
<td>43.7±0.77</td>
<td>44.1±0.79</td>
<td>43.4±0.75</td>
<td>0.22</td>
</tr>
<tr>
<td>VAS for treatment satisfaction, Mean±SD</td>
<td>4.78±0.14</td>
<td>4.72±0.16</td>
<td>4.84±0.12</td>
<td>0.39</td>
</tr>
<tr>
<td>PPBC Scale, Mean±SD</td>
<td>3.93±0.17</td>
<td>3.91±0.20</td>
<td>3.95±0.15</td>
<td>0.73</td>
</tr>
</tbody>
</table>

HRQoL = Health Related Quality of Life; VAS = Visual Analog Scale; PPBC = Patient Perception of Bladder Condition
other kinds of antimuscarinics are not licensed or easily achievable in Turkey. 5mg dosage of solifenacin would be more tolerable than 10mg for the long-term treatment of OAB symptoms.

The reason why we included women over the age of 40 in our study is to exclude women who were still in desire to have a child. Both drugs in our study were category C in pregnancy, therefore we aimed to select women without an expectation of a child anymore.

Chapple et al. (4) discussed the efficacy and safety of mirabegron by comparing 50mg and 100mg dosage with tolterodine 4mg over 2444 patients in 12 month follow-up and concluded that mirabegron was safe and effective in the long-term treatment of OAB. Marcelissen et al. (3) conducted a literature review including 10 studies and 3132 patients. The study concluded that patients with MUI were more likely to develop OAB symptoms after surgery for SUI as mentioned in our study (only 9 patients developed de novo OAB symptoms).

Similarly to our study, in a retrospective study including 342 women suffering from OAB symptoms, Schiavi et al. (11) compared efficacy and tolerability of mirabegron 50mg/day with solifenacin 5mg/day. Both drugs provided significant improvements in OAB symptoms. Detrusor overactivity decreased similarly in both groups (from 58.3% to 13.1% in the solifenacin group, from 58% to 11% in the mirabegron group). However, solifenacin showed more side effects and mirabegron

### Table 3 - Parameters for Safety Assessment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patient</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (n)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertensive Event (n)</td>
<td>12</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac Arrhythmia (n)</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Prolonged QT Interval (n)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nasopharyngitis (n)</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Headache (n)</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Sinusitis (n)</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Backpain (n)</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia (n)</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea (n)</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Constipation (n)</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Dry Mouth (n)</td>
<td>11</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>UTI (n)</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>AUR (n)</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Syncope (n)</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Nephrotoxicity (n)</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hepatotoxicity (n)</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Cognitive Impairment (n)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Side Effects in Total (n)</td>
<td>53</td>
<td>20</td>
<td>33</td>
</tr>
</tbody>
</table>

UTI = Urinary Tract Infection; AUR = Acute Urinary Retention
was recommended as a good option for long-term treatment of OAB. To our knowledge, the largest OAB study to date was conducted by Herschorn et al. (12) (SYNERGY Study) They evaluated the efficacy of combination therapy with mirabegron and solifenacin, comparing with monotherapy and placebo. 3398 patients were divided into 6 groups as placebo, solifenacin 5mg, mirabegron 25mg, mirabegron 50mg, solifenacin 5mg+mirabegron 25mg, solifenacin 5mg+mirabegron 50mg. After 18 weeks, the results showed that both of monotherapies were superior in efficacy to placebo and combination therapies superior to monotherapies, and the differences were statistically significant. (p <0.05) There was no significant difference in efficacy between solifenacin 5mg/day, mirabegron 25 mg/day and mirabegron 50mg/day monotherapies. However, solifenacin had more adverse effects than mirabegron. Our results are compatible with these studies. Both drugs provided significant improvements in OAB symptoms in our study, however mirabegron showed better tolerability than solifenacin particularly after 6 months of treatment, because of the significant side effects of solifenacin, primarily dry mouth.

Limitations of the study

Although according to our power analysis we have adequate sample size, our population is small. The main reason of this is the low socio-cultural status and rate of literacy of the female population in this region of our country. Therefore, it was hard to find sufficient number of patients who were enabled to understand and accept the study protocol. Additionally, we could include several types of antimuscarinics in our study so that a more decisive result about the efficacy and tolerability of mirabegron would be determined. However, according to the health insurance in our government, most of the patients are not enable to achieve most of the anti-muscarinics.

Twelve months seem to be adequate to find out the safety and tolerability of mirabegron, however, longer follow-up would reveal whether any tolerance may develop to its efficacy or a dose increase may be required.

Some patients may still have residual SUI after surgery. Severity of SUI as assessed by number of pads used a day is an important predictor of the surgery outcome. We were not enable to provide adequate information from the participants about this topic. Although majority of the participants benefited from surgery, severity of SUI before surgery may affect postinterventional urinary complaints so as OAB symptoms. Moreover, evaluation of prior treatments for OAB would significantly contribute to the quality of the study but the data is lacking.

The study results provided that mirabegron was an effective treatment option for OAB symptoms after surgery for SUI. Safety assessments showed similar results for both drugs but tolerability was significantly better for mirabegron particularly after 6 months of treatment when most patients using solifenacin reported to suffer from dry mouth or constipation. Relatively less and acceptable side effects of mirabegron make it a tolerable drug for long-term treatment of UUI (13).

CONCLUSIONS

In this study, we highlight that mirabegron is safe, effective and tolerable in the long-term treatment of OAB symptoms in females after surgery for SUI. In order to provide more definitive recommendations, more studies including larger sample sizes, more types of drugs and longer periods of follow-up are required.

CONFLICT OF INTEREST

None declared.

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E-mail: metezkd@gmail.com
Association between enuresis and obesity in children with primary monosymptomatic nocturnal enuresis

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ABSTRACT

Objective: The purpose of this study was to determine whether the presence of obesity was related with symptoms of nocturnal enuresis (NE) and the efficacy of behavioral intervention in the treatment of NE.

Materials and Methods: The patients diagnosed with primary monosymptomatic nocturnal enuresis (PMNE) were studied retrospectively. NE severity was classified as mild, moderate, and severe according to the frequency of enuresis. The children were divided into three groups, namely normal weight (5th-84th percentile), overweight (85th-94th percentile), and obesity (≥95th percentile), according to their Body Mass Index (BMI) percentage. The relationship between obesity level and enuresis severity was analyzed. After three months of behavioral therapy, the efficacy of treatment among normal, overweight, and obese groups were evaluated. Moreover, the predictive risk factors for treatment failure were investigated.

Results: The rates of severe enuresis in patients with normal weight, overweight, and obesity were 63.9%, 77.5%, and 78.6%, respectively. Obese children depicted higher odds of having severe enuresis compared with normal-weight children (OR: 1.571; 95% confidence interval [CI]: 1.196-2.065; P=0.001). The odds of presenting with severe enuresis were 1.99 times higher in children who are obese or overweight compared to children with normal weight (OR: 1.994; 95% CI: 1.349-2.946; P=0.001). The complete response of the normal group was higher than those of the overweight and obese groups (26.8% vs. 14.0%, P=0.010; 26.8% vs. 0.0%, P=0.000). Overweight children showed higher complete response than obese ones (14.0% vs. 0.0%, P=0.009). Logistic regression analysis revealed that obesity level and enuresis frequency were significantly related to the treatment failure of behavioral intervention.

Conclusions: Obesity is associated with severe enuresis and low efficacy of behavioral therapy in children with nocturnal enuresis.

INTRODUCTION

Nocturnal enuresis (NE) is the most common pediatric urological developmental disorder (1). The prevalence of enuresis is up to 20% in children aged 5 years old, and severe enuresis can persist indefinitely with prevalence rate of 2%-3% in adulthood (2, 3). Primary monosymptomatic nocturnal enuresis (PMNE) occurs in children who have previously been dry for <6 months wi-
without any (other) lower urinary tract symptoms or a history of bladder dysfunction (4). Although many different underlying pathophysiological mechanisms have been proposed to explain NE, its etiology remains unclear (5-8).

Obesity is a common and growing problem worldwide. According to Freedman et al., childhood obesity negatively affects blood pressure, lipid profiles, glucose metabolism, and cardiovascular diseases (9). Obese children are more likely affected by some other health problems, such as respiratory diseases, infertility, degenerative joint diseases, proteinuria, depression, anxiety, and discrimination in social life and the workplace, as compared with non-obese ones (10).

Obesity is related to the prevalence of enuresis and the treatment response of enuresis (11-13). However, analysis on the relationship between the symptoms of enuresis and obesity is lacking. In addition, the relations between enuresis and obesity have been controversial, including the association between body mass index (BMI) and therapeutic efficacy in the treatment of enuresis. According to several scholars, obesity and NE are not associated (14-16). Hence, further research evaluating the association between obesity and enuresis is needed to understand the possible role of obesity in the pathogenesis and treatment responses of enuresis.

This study aims to assess the association between obesity and enuresis, including the relationship of symptom classification of enuresis and the treatment responses of behavioral therapy for obese enuretic patients. The relationship between treatment failure and possible risk predictive variables is also analyzed.

**MATERIALS AND METHODS**

**Participants and methods**

This study was approved by the ethics committee of Beijing Children’s Hospital and was designed in accordance with the Declaration of Helsinki. The participants were children and adolescents who were referred from the enuresis outpatient clinic in Beijing Children’s Hospital between May 2016 and December 2017 and who had been diagnosed with PMNE. Consent forms were signed by their parents or caregivers. The inclusion criteria were as follows: PMNE without previous treatment of any kind during the past 6 months, aged between 5 and 15 years old, and signed informed consent. Exclusion criteria were defined as known anatomical, urological, gastrointestinal, cardiovascular, endocrinological, and/or neurological pathologies, and abnormalities in abdominal ultrasound or urinalysis that would interfere with evaluation. Demographic and disease characteristics, including age, gender, weight, height, family history of enuresis, frequency of enuresis, daytime lower urinary tract symptoms (such as urinary urgency, urinary frequency, and daytime urinary incontinence), and any treatment for NE were assessed by a questionnaire administered to the parents. After history taking and physical examination, all participants underwent urine analysis, urine culture, and urinary tract ultrasound. Patients with abnormal results were excluded. NE severity was categorized as mild, moderate, and severe according to the frequency of enuresis. NE every night or 5-6 wet nights a week was defined as severe, 1 or 2 days a week was considered mild, and somewhat in between was regarded as moderate.

BMI was calculated using the formula weight/height² (kg/m²). In this study, the standardized growth curve of Chinese children and adolescents aged 0-18 years established by Li et al. was used (17). The children were divided into three groups, namely normal weight (5th-84th percentile), overweight (85th-94th percentile), and obesity (≥95th BMI percentile), according to their BMI percentage (18).

Behavioral intervention is the first line of treatment and pharmacotherapy should not be initiated in children unless nonpharmacological interventions have failed. Behavioral intervention strategies involve educating families regarding enuresis and its treatment, offering suggestions for voiding patterns and frequency, limiting fluid intake, carrying the child to the toilet at night or waking the child up for urination, providing daily motivation and exercises aimed at
increasing bladder capacity, and treating constipation when present. The child must have an active role in bed cleaning after bed-wetting, should never be punished for wetting his/her bed, and must be rewarded if he/she reached the goal, as monitored by the signed wet and dry nights in a calendar. All patients were required to record daytime and overnight bladder diaries. If the patients experienced any difficulty, they sought help from their parents. We evaluated the efficacy of treatment in 3 months among the three groups after the start of behavioral therapy on the basis of the voiding diary kept by patients or their parents. Night-time urine volume was calculated as the weight of diapers plus the first voided volume in the morning. The presence of nocturnal polyuria was defined as an average night-time urine volume exceeding 130% of expected bladder capacity (30 + [age in years × 30] mL) (4, 19). The treatment response was defined by the 2014 ICCS criteria as follows: no response, partial response (<50% reduction of wet nights, 50%-99% reduction in the frequency of NE), and complete response (100% reduction of enuresis episodes) (20). Moreover, the predictive risk factors for treatment failure (partial response and no-response) were investigated.

### Statistical analysis

Statistical analyses were performed using the SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Univariate logistic regression and Pearson chi-square test were conducted to investigate the possible relationship between enuresis severity and obesity level. Enuretic patients were stratified by age, and chi-square test was then used to compare the differences in the treatment responses among patients aged 11-15 years and 5-10 years. Multivariable logistic regression model was performed to identify risk factors among age, gender, frequency of enuresis, degree of obesity, family history of enuresis, presence of nocturnal polyuria, and treatment failure. A P value less than 0.05 was considered statistically significant.

### RESULTS

A total of 666 patients with PMNE were included in this study. Demographic information of these participants is shown in Table-1. The children were aged 5-14.5 years with a median age (interquartile range) of 6.5 (5.1-9.1) years. No significant differences on age, gender, family history of enuresis, and nocturnal polyuria were found among normal, overweight, and obese groups (Table-1).

<table>
<thead>
<tr>
<th>Table 1 - Baseline clinical characteristics and demographic features.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>5-9</td>
</tr>
<tr>
<td>10-15</td>
</tr>
<tr>
<td>Family history of NE</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Nocturnal polyuria</td>
</tr>
<tr>
<td>Present</td>
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<td>Absent</td>
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</tbody>
</table>
A total of 214 patients (32.2%) had mild-moderate NE, and 452 (67.8%) had severe NE. The rates of severe enuresis in patients with normal weight, overweight, and obesity were 63.9%, 77.5%, and 78.6%, respectively. The rate of severe enuresis in patients with normal weight was lower than that in overweight children, and the difference was statistically significant (P=0.005, adjusted P-value=0.0125). No statistically significant differences were found in the rate of severe enuresis between obese and overweight groups and between obese and normal groups (P=0.864; P=0.015). The relationship between NE severity and the presence of obesity is shown in Table-2. Obese children depicted higher odds of having severe enuresis compared with normal-weight children (OR: 1.571; 95% confidence interval [CI]: 1.196-2.065; P=0.001). The odds of presenting with severe enuresis were 1.99 times higher in children who were obese or overweight compared to children with normal weight (OR: 1.994; 95% CI: 1.349-2.946; P=0.001).

Among the 666 patients, 48 did not follow the doctor’s advice, 32 did not regularly consult a doctor, and 28 were lost to follow-up. Thus, a total of 558 participants completed this treatment phase. The complete response of the normal group was higher than those of the overweight and obese groups, and the differences were statistically significant (26.8% vs. 14.0%, P=0.010; 26.8% vs. 0.0%, P=0.000). Overweight children showed higher complete response than obese ones, and the difference was statistically significant (14.0% vs. 0.0%, P=0.009). Among the 5-to 10-year-old patients, the complete response of the obese group was lower than that of the normal group (P=0.000); however, no significant differences were found regarding complete response between the normal and overweight groups and between the overweight and obese groups (P=0.045, P=0.019, adjusted P-value=0.0125). Among the 11- to 15-year-old patients, the complete response of the normal group was higher than that of the overweight group (P=0.007). However, no statistically significant differences were observed in the complete response between the normal and obese groups and between the overweight and obese groups (P=0.026, P=0.016, adjusted P-value=0.0125, Table-3).

Multivariable logistic regression analysis of predictive risk factors for treatment failure.

A logistic regression model was used to investigate the relationship between treatment failure and possible risk predictive variables by using six factors (age, gender, frequency of NE, family history of NE, presence of nocturnal polyuria, and obesity) as independent variables and treatment failure as a dependent variable (Table-4). Logistic regression analysis revealed that obesity level (OR: 2.633, 95% CI: 1.615-4.291) and enuresis frequency (OR: 3.350, 95% CI: 2.082-5.390) were significantly related to the treatment failure of behavioral therapy.

**DISCUSSION**

NE has been found to be related to obesity. Overweight and obese children tend to consume an unhealthy diet that may overwhelm their functional bladder capacity and result in NE (21, 22). Weintraub et al. reported that NE affects 9% of children with normal weight, 16% of overweight children, and 30% of obese children and adolescents (7-18 years old) (12). Their results also showed that the odds ratio of enuresis in obese children was 6.5 folds more than that in nor-

### Table 2 - The relationship between enuresis severity and the presence of obesity.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mild-moderate n (%)</th>
<th>Severe n (%)</th>
<th>Total n (%)</th>
<th>X²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal n (%)</td>
<td>172 (36.1%)</td>
<td>304 (63.9%)</td>
<td>476 (100.0%)</td>
<td>12.279</td>
<td>0.002</td>
</tr>
<tr>
<td>Overweight n (%)</td>
<td>27 (22.5%)</td>
<td>93 (77.5%)</td>
<td>120 (100.0%)</td>
<td>12.279</td>
<td>0.002</td>
</tr>
<tr>
<td>Obese n (%)</td>
<td>15 (21.4%)</td>
<td>55 (78.6%)</td>
<td>70 (100.0%)</td>
<td>12.279</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Table 3 - The treatment responses of behavioral therapy.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Nonresponse n (%)</th>
<th>Partial Response n (%)</th>
<th>Complete Response n (%)</th>
<th>X²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal n (%)</td>
<td>67 (17.4%)</td>
<td>214 (55.7%)</td>
<td>103</td>
<td>28.314</td>
</tr>
<tr>
<td>5-15 years</td>
<td>Overweight n (%)</td>
<td>18 (15.8%)</td>
<td>80 (70.2%)</td>
<td>16</td>
<td>22.205</td>
</tr>
<tr>
<td></td>
<td>Obese n (%)</td>
<td>12 (20.0%)</td>
<td>48 (80.0%)</td>
<td>0</td>
<td>14.071</td>
</tr>
<tr>
<td></td>
<td>Normal n (%)</td>
<td>46 (16.0%)</td>
<td>164 (56.9%)</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>Overweight n (%)</td>
<td>16 (21.6%)</td>
<td>48 (64.9%)</td>
<td>10</td>
<td>12.351</td>
</tr>
<tr>
<td></td>
<td>Obese n (%)</td>
<td>8 (17.0%)</td>
<td>39 (83.0%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal n (%)</td>
<td>21 (21.9%)</td>
<td>50 (52.1%)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>11-15 years</td>
<td>Overweight n (%)</td>
<td>2 (5.0%)</td>
<td>32 (80.0%)</td>
<td>6</td>
<td>14.071</td>
</tr>
<tr>
<td></td>
<td>Obese n (%)</td>
<td>4 (30.8%)</td>
<td>9 (69.2%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 - Logistic regression analysis on therapeutic effect of behavioral therapy.

<table>
<thead>
<tr>
<th>Factors</th>
<th>B</th>
<th>Standard error</th>
<th>Wald value</th>
<th>P value</th>
<th>OR</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Gender</td>
<td>0.093</td>
<td>0.233</td>
<td>0.159</td>
<td>0.690</td>
<td>1.097</td>
<td>0.694 - 1.734</td>
</tr>
<tr>
<td>Age</td>
<td>0.032</td>
<td>0.276</td>
<td>0.013</td>
<td>0.909</td>
<td>1.032</td>
<td>0.600 - 1.774</td>
</tr>
<tr>
<td>Enuresis frequency</td>
<td>1.209</td>
<td>0.243</td>
<td>24.816</td>
<td>0.000</td>
<td>3.350</td>
<td>2.082 - 5.390</td>
</tr>
<tr>
<td>Family history of NE</td>
<td>-0.428</td>
<td>0.237</td>
<td>3.263</td>
<td>0.071</td>
<td>0.652</td>
<td>0.410 - 1.037</td>
</tr>
<tr>
<td>Nocturnal polyuria</td>
<td>-0.001</td>
<td>0.218</td>
<td>0.000</td>
<td>0.995</td>
<td>0.999</td>
<td>0.651 - 1.531</td>
</tr>
<tr>
<td>Obesity level</td>
<td>0.968</td>
<td>0.249</td>
<td>15.075</td>
<td>0.000</td>
<td>2.633</td>
<td>1.615 - 4.291</td>
</tr>
</tbody>
</table>

mal weight children. Guven et al. and Sally et al. analyzed the effect of obesity on the treatment responses of enuresis, but their conclusions were contradictory (13, 16). This finding led us to investigate a possible association between obesity and enuresis in children and adolescents. In the present study, we examined the relationship between enuresis severity and obesity degree, which has not been explored in previous studies.

In our study, children who are obese and overweight were more likely to develop severe enuresis compared with those with normal weight. Some common pathogenesis for obesity and enuresis may explain this result. First, obesity exposes the pelvic floor to elevated intra-abdominal and intra-vesical pressure, thereby compromising the functional bladder capacity (23). This reduced functional bladder capacity plays an important role in the pathogenesis of enuresis. Second, monosymptomatic NE occurs after psychological stress or trauma and results in increased psychological distress for the child (24). Obese children are also under higher psychological distress than their non-obese peers (25). Obesity and enuresis are closely related to psychological factors, indicating that several shared mechanisms may be involved in their pathogenesis. Third, obesity is associated with hyperglycemia, which can cause diuresis and lower urinary tract symptoms. Fourth, adolescent obesity is related with sleep-disordered breathing (SDB) conditions, such as habitual snoring, obstructive sleep apnea (OSA), upper airway resistance syndrome, and hypoventilation (26-28). SDB is directly related to NE. Habitual snorers are
at a greater risk of having NE than non-snorers (29). Moreover, bedwetting is predictive of OSA in children (30). The association between SDB and enuresis may be explained by large amounts of overnight sodium and urine excretion, which are probably caused by the increased secretion of atrial natriuretic peptide in patients with SDB (31). Thus, explaining the association between obesity and severe enuresis is not difficult.

In this study, the incidence of complete response was lower in overweight and obese patients than in normal-weight enuretic patients. Moreover, the level of obesity (OR: 2.633, 95% CI: 1.615-4.291) was an independent risk factor for the treatment failure of behavioral therapy. This result was consistent with previous studies. Guven et al. observed a good response to standard treatment in patients with a BMI below the 85th percentile (13). They speculated that the low treatment success rates in patients with high BMI suggest that obesity and incontinence may share a common etiology. Obesity is related to hormonal abnormalities in some children, and NE may be associated with an abnormality of antidiuretic hormone secretion (10, 32). Hence, pituitary or other central nervous system abnormality could be the cause of both conditions. Kovacevic et al. also reported that the low response rate in patients with NE is associated with obesity (33). Obese children often suffer from SDB, which is closely correlated with NE (34). The association between enuresis and SDB in children is supported by the decrease in enuresis frequency or even by the complete resolution of enuresis after the successful treatment of SDB (35). Although we did not evaluate this condition in our study, obesity may have increased the NE via the mechanism of SDB and negatively affected the treatment outcomes.

In our study, multivariable logistic regression analysis revealed that enuresis frequency (OR: 3.350, 95% CI: 2.082-5.390) was significantly related to the treatment failure of behavioral therapy. This result is in line with previous findings. Kurt et al. reported that NE frequency is a predictive factor in estimating the effectiveness of behavioral treatment (36). In their study, nearly half of the patients who had all days or 5-6 days of enuresis in a week did not show any response to behavioral interventions. Similarly, Önol et al. showed that NE severity is an independent risk predictor of complete response (37).

In view of the above findings of this study, some suggestions may be helpful in guiding clinical practice. First, although losing weight is fraught with difficulties and challenges, weight control should be attempted as the initial step in obese children with NE. Second, obesity is associated with an unhealthy diet. Ferrara et al. reported that specific dietary advices can effectively manage PMNE (38). Thus, dietary recommendations may be necessary for enuretic children with obesity. Third, a previous study suggested that obesity is associated with a low rate of voiding diary completion (13). In this case, behavioral intervention, including alarm therapy, may be prone to failure. Pharmacological intervention might be appropriate. Fourth, several medical conditions, such as SDB, psychopathological disorders, and type 2 diabetes mellitus, co-occur at increased rates among obese and enuretic children. Therefore, the active treatment of comorbidity may be beneficial to the remission of both in some extent.

The limitations of this study are as follows: First, risk factors affecting treatment response, which are indicators for detrusor overactivity (e.g., bladder wall thickness, and bladder volume), have not been analyzed and thus must be investigated in the future. Second, this study reveals an association between enuresis and obesity, but does not prove the cause and effect. Third, the duration of behavioral therapy is only for 3 months. Further study is needed to clarify the role of obesity in the efficacy of long-term behavioral intervention.

In conclusion, obesity is associated with severe enuresis and low efficacy of behavioral therapy in children with NE. Obesity should be considered in enuretic patients, especially if they display severe symptoms of enuresis or they fail to respond to behavioral therapy.

**CONFLICT OF INTEREST**

None declared.
REFERENCES


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Voiding symptoms obtained by open versus directed anamnesis as predictors of voiding dysfunction in women

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ABSTRACT

Objectives: To determine the differences between voiding symptoms obtained by open anamnesis (VS-Open) versus voiding symptoms obtained by directed anamnesis (VS-Directed) to predict voiding dysfunction in women.

Materials and Methods: Retrospective study of women with prior anti-incontinence surgery evaluated during 5 years. In a standardized clinical history taking, each patient was asked to answer question number five of the UDI-6 questionnaire (“Do you experience any difficulty emptying your bladder?”). If the answer was positive, the following voiding symptoms spontaneously described by the patient were documented: slow urine stream, straining to void, intermittent stream and feeling of incomplete bladder emptying, which were considered VS-Open. If the answer to this question was negative or if the patient had not reported the four voiding symptoms, she was asked in a directed manner about the presence of each of them, which were considered VS-Directed. Voiding dysfunction was considered the presence of a maximum flow ≤ 12 mL/s and/or a postvoid residual > 100 mL.

Results: Ninety-one women are analyzed. Eighteen patients presented voiding dysfunction (19.8%). There was a statistical association between voiding dysfunction and the presence of any VS-Open (p = 0.037) and straining to void obtained by open anamnesis (p = 0.013). Sensitivity, specificity, PPV, NPV, positive likelihood ratio and negative likelihood ratio, respectively, were 44.4% and 27.8%, 80.8% and 94.5%, 36.3% and 55.6%, 85.5% and 84.1%, 2.324 and 5.129, and 0.686 and 0.764. There was no statistical association between voiding dysfunction and VS-Directed.

Conclusions: VS-Open may predict better voiding dysfunction than VS-Directed in women.

INTRODUCTION

Large epidemiologic studies have demonstrated that the prevalence of voiding symptoms in women ranges between 14.9 and 19.5%, and that these are generally related to storage symptoms (1, 2). The NICE (The National Institute for Health and Care Excellence, U.K.) guidelines for management of urinary incontinence in women confers value to the presence of “symptoms suggestive of voiding dysfunction” and recommends the performance of a multichannel urodynamics assessment.

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before undergoing anti-incontinence surgery in women presenting with such symptoms (3).

Several studies have aimed at correlating voiding and/or post-micturition symptoms with voiding dysfunction in women, and have found difficulties at establishing such correlation. On one hand, there is a lack of consensus regarding the definition and diagnosis of voiding dysfunction in females (4), and there are studies that use only one criterion, such as either the urinary flow rate decrease or the increased post-void residual volume (PVR) (5-8). On the other hand, symptoms may be retrieved either through a medical interview (5, 6, 9-11) or through the implementation of standardized questionnaires (1, 2, 7, 12), thus generating variations in their value to predict voiding dysfunction.

In their most recent terminology report, the International Urogynecological Association (IUGA) and the International Continence Society (ICS) define voiding dysfunction as an abnormally slow and/or incomplete voiding and recommend it is studied with the use of uroflowmetry and PVR measurement, although there is still no consensus on the values that are considered as abnormal (13).

The purpose of the present exploratory work is to study whether the voiding symptoms are predictive for voiding dysfunction in women in accordance with the definition of the main international societies, and to define whether there are differences between voiding symptoms obtained by open anamnesis (VS-Open) versus voiding symptoms obtained by directed anamnesis (VS-Directed).

**MATERIALS AND METHODS**

We retrospectively reviewed an electronic database of patient’s medical records in a university referral center. Patient information was collected and entered into a database at the time of history taking, and before conducting urodynamics according to ICS and IUGA definitions and recommendations (13-15). All patients provided informed consent for the use of their clinical information in research studies, and the confidentiality of the data was guaranteed. The project was approved by the Institutional Scientific Ethics Committee of our institution.

As part of a standardized clinical history procedure performed before every urodynamic study by the two urologist directly involved, each patient was asked to answer question number five of the Urogenital Distress Inventory Short Form Questionnaire (UDI-6) (“Do you experience any difficulty emptying your bladder?”) (16). If the answer was positive, the following voiding symptoms spontaneously described by the patient were documented: 1) slow urine stream, 2) straining to void, 3) intermittent stream (intermittency) and 4) a feeling of incomplete bladder emptying (according to the ICS, incomplete bladder emptying is a post-micturition symptom) (14). Any or all of the symptoms expressed spontaneously were considered VS-Open. If the answer to this question was negative or if the patient had not spontaneously reported experiencing the four voiding symptoms, she was asked in a directed manner about the presence of each of them. These symptoms were considered VS-Directed (VS-open were always described as VS-Directed subsequently). Symptoms were considered as either present or absent, with no severity stratification. All women with prior anti-incontinence surgery during 5 consecutive calendar years were selected, for being a group with a higher likelihood of presenting voiding dysfunction. The following exclusion criteria were applied: 1) pelvic organ prolapse over stage II, 2) “urethrolysis” surgery prior to the testing, 3) use of uroselective drugs, 4) neurological diseases, 5) bladder pain syndrome and 6) history of pelvic radiotherapy.

Urodynamic testing was performed in accordance with the recommendations of the ICS (15). First, a non-invasive uroflowmetry was performed in private and the PVR was measured through catheterization; the procedure was repeated in those patients presenting abnormal voiding testing or voiding volume <150 mL (until a proper volume was obtained). Subsequently, interactive filling cystometry was performed. A double lumen 6F urethro-vesical catheter was used for bladder filling and intravesical pressure measurement and a rectal 8F balloon catheter was used for abdominal pressure measurement. External pressure transducers were positioned at the upper edge of symphysis pubis and the system was zeroed to atmospheric pressure. Room temperature 0.9% sa-
line solution was infused at a rate of 70 mL/min. Pressure transmission was assessed with coughing at the beginning and at the end of each testing, every 1 minute, during the complete testing and before and after each major event, in order to correct artifacts immediately; this was the only method used to provoke detrusor overactivity. The stress test was conducted in a standardized and stepped manner, with the use of progressively increasing cough intensity, following successive stages in case of not evidencing urodynamic stress incontinence: 1) with 300 mL infused in the sitting position, 2) with 300 mL infused in standing position and 3) at the maximum cystometric capacity in standing position (with the corresponding change of the position of the transducers). In patients with maximum cystometric capacity of less than 300 mL, it was generally conducted at capacity in the sitting and the standing positions. The pressure-flow study was performed in private. Finally, the PVR was measured through the urethrovésical catheter.

The repeated presence of a maximum flow rate less than or equal to 12 mL/s and/or a PVR higher than 100 mL were considered as voiding dysfunction. The following was defined in the pressure-flow analysis: 1) bladder outlet obstruction was defined as a maximum flow rate ≤12 mL/s in association with detrusor pressure at maximum flow rate ≥25cm H₂O (17); 2) reduced detrusor contractility was defined as a maximum flow rate ≤12 mL/s in association with a detrusor pressure at maximal flow rate ≤10cm H₂O modified from Gotoh et al. (18) and 3) mixed voiding dysfunction was defined as a maximal flow rate ≤12 mL/s in association with a detrusor pressure at maximal flow rate between 11 and 24 cm H₂O, with a concordant free uroflowmetry in all cases. The Chi square test or the Fisher’s exact test were used to evaluate statistically significant association between voiding dysfunction and the presence of any vs-Open and vs-Directed. The procedure was applied likewise for each one of the symptoms individually. In case of obtaining a statistically significant result (p <0.05), the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and positive and negative likelihood ratio and strength of agreement were calculated using Cohen’s kappa coefficient. Data were processed with Stata 12.1 program® (StataCorp, 2012). Figure-1 shows a flowchart of the “Material and Methods” and Figure-2 shows a flowchart of the standardized clinical history procedure performed before every urodynamic study.

RESULTS

From a total of 114 women with prior anti-incontinence surgery undergoing urodynamics, 23 were excluded (6 for having pelvic organ prolapse over stage II, 5 for prior “urethrolysis”, 6 for using uroselective drugs, 5 for neurological diseases and 1 due to bladder pain syndrome), and 91 patients underwent the analysis. All patients were evaluated 6 or more months after the anti-incontinence surgery. Table-1 displays the clinical history of the patients. Twenty-three patients had VS-Open, 70 patients had VS-Directed (including the 23 patients with VS-Open) and only 21 patients didn’t have any kind of voiding symptoms (23.1%). Table-2 shows urodynamic diagnoses of the patients according to urinary incontinence symptoms. Of the total, 18 patients presented voiding dysfunction (19.8%): 13 had bladder outlet obstruction, 3 had reduced detrusor contractility and 2 had mixed voiding dysfunction. There were 4 patients with PVR higher than 100 mL (22.2% of patients with voiding dysfunction), all with a maximal flow rate less than or equal to 12 mL/s. Table-3 displays statistically significant associations between the presence of voiding dysfunction and VS-Open and VS-Directed. Due to small numbers we are unable to describe variation in voiding symptoms according to the time elapsed since the surgery. There was a statistically significant association between voiding dysfunction and a) the presence of any VS-Open and b) straining to void obtained by open anamnesis. There was no statistically significant association between voiding dysfunction and VS-Directed. Table-4 shows sensitivity, specificity, PPV, NPV, accuracy, positive and negative likelihood ratio and strength of agreement (Cohen’s kappa) of symptoms with statistically significant association.
DISCUSSION

This exploratory study, despite being retrospective and that included a limited number of patients, has the strength to evaluate a homogeneous group of women in a standardized manner, with documentation of analyzed data upon examination, following the definitions and recommendations of the IUGA and the ICS.

Correlation between voiding and/or post-micturition symptoms and voiding dysfunction is difficult to assess due to a lack of consensus in the definition and diagnosis of voiding dysfunction and in the way symptoms are retrieved.

For the diagnosis of voiding dysfunction, some studies use only the criterion of decreased urinary flow rate (5) or just the increase in PVR criterion (6–8). Other studies use both criteria but independently of one another (11, 19), and this modifies all the results obtained. Additionally, there is another group of studies that only considers the bladder outlet obstruction diagnosis, without assessing those patients with a reduced detrusor contractility, thus having an impact on conclusions (10, 12, 20). The present study follows the IUGA and ICS definition, and therefore the voiding dysfunction diagnosis considers both a decreased urinary flow criterion as well as the criterion of increased PVR. However, any definition of voiding dysfunction in females has a certain degree of arbitrariness. We chose the criteria of maximal flow rate $\leq 12$ mL/s based on the main studies that use such cutoff to define bladder outlet obstruction in women when associated to high detrusor pressure at maximum flow rate (17, 21), that additionally coincides with the cutoff to define a reduced detrusor contractility when associated to low detrusor pressure at maximum flow rate described by Gotoh et al. (18). With regard to PVR, the IUGA/ICS joint report on the terminology for female pelvic floor dysfunction indicates different values for the upper limit of normal (30, 50 and 100 mL) (13). In the present study a value higher than 100 mL was chosen as abnormal. Such value is observed in only 5% of asymptomatic peri and post-menopausal women (22). Anyhow, in
Figure 2 - Flowchart of the standardized clinical history procedure performed before every urodynamic study (UDI-6: Urogenital Distress Inventory Short Form Questionnaire).

In the present study, all patients with increased PVR had decreased maximal flow rates, therefore the results would not have been affected if higher PVR criterion had been defined, a fact that cannot be guaranteed in studies that do not consider both criteria.

To be able to compare our results, focus must be only on the scant studies that diagnose voiding dysfunction with urinary flow rate and PVR criteria, and that also include not only bladder outlet obstruction but also reduced detrusor contractility. It is with this perspective that Groutz et al., applying a medical interview apparently in a directed manner to 206 women, assessed the presence of at least one voiding symptom (hesitancy, straining to void, intermittency, strength of urine stream, feeling of incomplete bladder emptying) and concluded that voiding dysfunction defined as a maximal flow rate less than 12 mL/s and/or a PVR higher than 150 mL (present in 40 patients) could be found in women with and without suggestive symptoms (in 21.2% and 16.5% respectively) (9). On the other hand, Hubeaux et al., using 5 items of the Bristol Female Lower Urinary Tract Symptoms Questionnaire (hesitancy, straining to void, intermittency, strength of urine stream, feeling of incomplete bladder emptying) in 93 women with genuine stress urine incontinence with no evident obstruction cause undergoing urodynamic testing, did not find an association with voiding dysfunction defined as a maximal flow rate less than 15 mL/s and/or a PVR higher than 50 mL and an abnormal pattern of the flow curve (23). Our study, that considered voiding dysfunction as the presence of a maximal flow rate less than or equal to 12 mL/s and/or a PVR higher than 100 mL, failed to find an association with VS-Directed, concurring with the study of Groutz et al., and similarly to the results of Hubeaux et al., if we consider that there is a similarity between asking about the presence of each symptom in a directed manner and applying a questionnaire that includes them all. Noteworthy, a reasonable association was found between voiding dysfunction and the presence of “any VS-Open” and with “straining to void obtained by open anamnesis” (Table-4). It is interesting to comment that Jeffery et al. also described the importance of the symptom...
Table 1 - Medical history in women with previous anti-incontinence surgery undergoing urodynamics (n = 91).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>62.7 ± 11.06 (34 – 81)</td>
</tr>
<tr>
<td>Vaginal deliveries (range)</td>
<td>2.79 ± 1.91 (0 – 11)</td>
</tr>
<tr>
<td>Previous hysterectomy</td>
<td>31 (35%)</td>
</tr>
<tr>
<td><strong>Type of anti-incontinence surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Mid-urethral sling</td>
<td>50 (54.9%)</td>
</tr>
<tr>
<td>Burch colposuspension</td>
<td>29 (31.9%)</td>
</tr>
<tr>
<td>Mid-urethral sling and Burch surgery</td>
<td>5 (5.5%)</td>
</tr>
<tr>
<td>Unknown vaginal surgeries</td>
<td>7 (7.7%)</td>
</tr>
<tr>
<td><strong>Symptoms of</strong></td>
<td></td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>11 (12.1%)</td>
</tr>
<tr>
<td>Urge urinary incontinence</td>
<td>20 (22.0%)</td>
</tr>
<tr>
<td>Mixed urinary incontinence</td>
<td>54 (59.3%)</td>
</tr>
<tr>
<td>Other types of urinary incontinence</td>
<td>6 (6.6%)</td>
</tr>
<tr>
<td><strong>VS-Open</strong></td>
<td>23 (25.3%)</td>
</tr>
<tr>
<td>Slow stream</td>
<td>5</td>
</tr>
<tr>
<td>Straining to void</td>
<td>9</td>
</tr>
<tr>
<td>Intermittent stream</td>
<td>13</td>
</tr>
<tr>
<td>Feeling of incomplete emptying c</td>
<td>3</td>
</tr>
<tr>
<td><strong>VS-Directed</strong></td>
<td>70 (76.9%)</td>
</tr>
<tr>
<td>Slow stream</td>
<td>20</td>
</tr>
<tr>
<td>Straining to void</td>
<td>15</td>
</tr>
<tr>
<td>Intermittent stream</td>
<td>24</td>
</tr>
<tr>
<td>Feeling of incomplete emptying c</td>
<td>45</td>
</tr>
</tbody>
</table>

| Without any voiding symptom           | 21 (23.1%)                           |

*a = Insensible urinary incontinence, nocturnal enuresis; b = VS-Open: voiding symptoms obtained by open anamnesis; c = A post micturition symptom according to ICS; d = VS-Directed: voiding symptoms obtained by directed anamnesis

“straining to void” as a predictor of voiding dysfunction, although they evaluated separately the maximal flow rate and the PVR. Through a standardized questionnaire applied to 116 patients, they evaluated the presence of voiding symptoms that occurred “more commonly than occasionally” (straining to void, double voiding, post-micturition leakage, slow urine stream and feeling of incomplete bladder emptying), and found that “straining to void” was the only predictor of decreased maximal flow rate (less than 15 mL/s) and of increased PVR (PVR higher than 100 mL and 150 mL) (11).

If the outcomes would be applied in the clinical practice, the “straining to void obtained by open anamnesis” almost ensures the diagnosis of voiding dysfunction (94.5% specificity, which is in-
Table 2 - Urodynamics results in women with previous anti-incontinence surgery according to the type of urinary incontinence symptoms (n = 91).

<table>
<thead>
<tr>
<th>Type of symptom</th>
<th>Filling cystometry</th>
<th>Pressure-flow study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress urinary incontinence (n = 11)</td>
<td>Urodynamic stress incontinence</td>
<td>11 (100%) Bladder outlet obstruction 2(18%)</td>
</tr>
<tr>
<td>Urge urinary incontinence a (n = 20)</td>
<td>Detrusor overactivity</td>
<td>11 (55%) Bladder outlet obstruction 4(20%)</td>
</tr>
<tr>
<td>Mixed urinary incontinence (n = 54)</td>
<td>Urodynamic stress incontinence Detrusor overactivity Mixed filling diagnosis b</td>
<td>21(39%) Bladder outlet obstruction 4(7.4%) Reduced detrusor contractility 3(5.6%) Mixed voiding dysfunction 1(1.9%)</td>
</tr>
<tr>
<td>Other types of urinary incontinence (n = 6)</td>
<td>Urodynamic stress incontinence</td>
<td>3 (50%) Bladder outlet obstruction 3(50%)</td>
</tr>
</tbody>
</table>

a = In patients only with urge urinary incontinence symptoms the stress test wasn't done; b = Mixed filling diagnosis: Urodynamic stress incontinence + Detrusor overactivity

Table 3 - Statistical associations between voiding dysfunction and voiding symptoms in women with previous anti-incontinence surgery.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS-Open a</td>
<td></td>
</tr>
<tr>
<td>Any spontaneous symptom</td>
<td>0.037</td>
</tr>
<tr>
<td>Slow stream</td>
<td>0.256</td>
</tr>
<tr>
<td>Straining to void</td>
<td>0.013</td>
</tr>
<tr>
<td>Intermittent stream</td>
<td>0.068</td>
</tr>
<tr>
<td>Feeling of incomplete emptying b</td>
<td>0.488</td>
</tr>
<tr>
<td>VS-Directed c</td>
<td></td>
</tr>
<tr>
<td>Any directed symptom</td>
<td>0.551</td>
</tr>
<tr>
<td>Slow stream</td>
<td>0.072</td>
</tr>
<tr>
<td>Straining to void</td>
<td>0.179</td>
</tr>
<tr>
<td>Intermittent stream</td>
<td>0.368</td>
</tr>
<tr>
<td>Feeling of incomplete emptying b</td>
<td>0.317</td>
</tr>
</tbody>
</table>

a = VS-Open: voiding symptoms obtained by open anamnesis; b = A post micturition symptom according to ICS; c = VS-Directed: voiding symptoms obtained by directed anamnesis.
Voiding symptoms to predict voiding dysfunction

As well as patients with stress-predominant urinary incontinence, this symptom would help to determine the need of a full urodynamic study to evaluate voiding dysfunction, which is associated with obvious worse surgical outcomes (the ValUE trial reported that 11.9% of the patients of the urodynamic-testing group had voiding dysfunction despite having a PVR less than 150 mL and that these patients had less satisfactory outcomes (62.1% vs. 78.3%) [24]. Finally, we have to be careful with the interpretation of the high NPV of “any VS-Open” and “straining to void obtained by open anamnesis”: without considering any voiding symptom our cohort has a 80.2% probability of not having voiding dysfunction (19.8% patients with voiding dysfunction), which increases only to 85.5% if the patient reports “any VS-Open” and to 84.1% if the patient reports “straining to void by open anamnesis”.

CONCLUSIONS

This study shows that VS-Open may predict better voiding dysfunction than VS-Directed in women. To date, we are not aware of prior publications having studied this matter. Additional larger and prospective studies are required to confirm these findings.

ABBREVIATIONS

VS-Open = voiding symptoms obtained by open anamnesis
VS-Directed = voiding symptoms obtained by directed anamnesis
PVR = post-void residual volume
PPV = positive predictive value
NPV = negative predictive value
CI = Confidence interval

Table 4 - Voiding symptoms as predictors of voiding dysfunction in women with previous anti-incontinence surgery.

<table>
<thead>
<tr>
<th></th>
<th>Any voiding symptom by open anamnesis</th>
<th>Straining to void by open anamnesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>44.4%</td>
<td>27.8%</td>
</tr>
<tr>
<td>Specificity</td>
<td>80.8%</td>
<td>94.5%</td>
</tr>
<tr>
<td>PPV</td>
<td>36.3%</td>
<td>55.6%</td>
</tr>
<tr>
<td>NPV</td>
<td>85.5%</td>
<td>84.1%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>73.6%</td>
<td>81.3%</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>2.324</td>
<td>5.129</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.686</td>
<td>0.764</td>
</tr>
<tr>
<td>Kappa (95% CI)</td>
<td>0.233 (0.006–0.460)</td>
<td>0.275 (0.029–0.521)</td>
</tr>
</tbody>
</table>

PPV = Positive predictive value; NPV = Negative predictive value; CI = Confidence interval

CONFLICT OF INTEREST

None declared.

REFERENCES


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Vesicostomy button: how is it placed, in whom, and how is quality of life affected?

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1 University of California, San Diego, CA, USA; 2 Rady Children’s Hospital, San Diego, CA, USA

ABSTRACT

Purpose: The vesicostomy button has been shown to be a safe and effective bladder management strategy for short- or medium-term use when CIC cannot be instituted. This study reports our use with the vesicostomy button, highlighting the pros and cons of its use and complications. We then compared the quality or life in patients with vesicostomy button to those performing clean intermittent catheterization.

Materials and Methods: Retrospective chart review was conducted on children who had a vesicostomy button placed between 2011 and 2015. Placement was through existing vesicostomy, open or endoscopically. We then evaluated placement procedure and complications. A validated quality of life questionnaire was given to patients with vesicostomy button and to a matched cohort of patients performing clean intermittent catheterization.

Results: Thirteen children have had a vesicostomy button placed at our institution in the 4 year period, ages 7 months to 18 years. Indications for placement included neurogenic bladder (5), non-neurogenic neurogenic bladder (3), and valve bladders (5). Five out of 7 placed via existing vesicostomy had leakage around button. None of the endoscopically placed buttons had leakage. Complications were minor including UTI (3), wound infection (1), and button malfunction/leakage (3). QOL was equal and preserved in patients living with vesicostomy buttons when compared to CIC.

Conclusion: The vesicostomy button is an acceptable alternative to traditional vesicostomy and CIC. The morbidity of the button is quite low. Endoscopic insertion is the optimal technique. QOL is equivalent in patients with vesicostomy button and those who perform CIC.

INTRODUCTION

The vesicostomy button is an adaptation of the gastrostomy button placed into the bladder. It was first described as a means of bladder drainage in 1996 and became popularized by our European colleagues in 2007 (1-3). The vesicostomy button is an attractive option for those patients in which clean intermittent catheterization (CIC) cannot be instituted. CIC is not feasible in some children due to anatomic variations, neurologic reasons, or pain and discomfort from catheter insertion. It has been well established that the goals of bladder management include preservation of the upper tracts, low pressure storage, and a socially acceptable means of drainage. CIC has been the gold standard owing to low risk of infection, stone formation, and erosion (4). Alternatives to...
CIC have been investigated including continuous indwelling Foley catheter, suprapubic tube, Mitrofanoff vesicostomy, and the vesicostomy button; each modality has unique risks and benefits and can be chosen with appropriate physician and family discussion (1).

The vesicostomy button ideally allows the patient to enjoy the benefits of urinary continence with intermittent bladder drainage without the use of a bag or catheter insertion. Placement can be done by an open technique, endoscopic technique, percutaneous technique, or insertion into an established vesicostomy tract (2). The literature has shown the vesicostomy button is a safe and effective alternative with minor complications including leakage around the button, local wound infections, and UTIs; no major complications were reported.

Improving quality of life for pediatric patients in an important consideration for pediatric urologists. Quality of life impacts care options and surgical decisions. Milliken et al. (5) postulated an improved quality of life in children managed with the vesicostomy button, owing to ease of use and discretion, however no study has objectively assessed the impact of using the vesicostomy button on quality of life.

We aim to discuss our experience with the vesicostomy button focusing on patient selection factors, technique of placement, and complications associated with the vesicostomy button. We also evaluated quality of life of the button and compared it to CIC patients. We hypothesized that quality of life would be improved with vesicostomy button use.

**MATERIALS AND METHODS**

Institutional Review Board approval was obtained. A retrospective chart review was conducted on children who had a vesicostomy button placed between 2011 and 2015. Data collected included patient name, age, presentation to urology, underlying diagnoses, indication for vesicostomy button placement, length of placement at time of review, complications at the first follow-up after placement, complications within the first 30 days after placement, UTI's 12 months before and after placement up to the date of review, creatinine before and after placement, and upper tract imaging.

We also prospectively identified patients undergoing CIC and matched them to the vesicostomy button patients by age and gender. A validated Intermittent Self-Catheterization Questionnaire (ISC-Q) was administered to the patient or family during a scheduled clinic visit (6). The ISC-Q is a self-report survey that focuses on quality of life (Figure-1). The survey was adapted to vesicostomy button with 5 questions eliminated that relate to the single use nature of a urethral catheter. The adapted ISC-Q includes 19 items that evaluate 4 domains: ease of use, convenience, discreteness and psychological well-being. Patients and/or primary caregivers were encouraged to fill out the questionnaire depending on age and cognitive ability or the participant.

**Technique for primary placement: open technique**

The open placement is performed via 2-3cm incision 2 finger breadths above the pubic symphysis. A cystotomy is created to accommodate an 18-French catheter. The button is then directly inserted into the bladder, the balloon is inflated, and a purse-string absorbable suture is placed to create a snug fit of the detrusor and mucosa around the button. The button is the exact button used for gastrostomy tubes and comes with extension tubing that attaches to the button. To drain the bladder the extension tubing is connected and can drain directly into toilet or urinal (Figure-2).

**Technique for primary placement: Endoscopic/Percutaneous Technique**

Patient is positioned into dorsal lithotomy position and the appropriate cystoscope is inserted into the bladder. The dome of the bladder is visualized. A small skin incision is made and a finder needle is inserted followed by a 0.038 wire under direct vision. The finder needle is removed leaving the wire in place; dilators are then passed over the wire to a maximum of 18-French. A vesicostomy button measuring device is used to measure the length of the tract and chose the appropriate button size. The vesicostomy button is placed over the wire under direct vision.
Figure 1 - Intermittent Self-Catheterization Questionnaire (ISC-Q) adapted for Vesicostomy (Mic-Key) Button Users.

<table>
<thead>
<tr>
<th></th>
<th>Strongly disagree</th>
<th>Slightly disagree</th>
<th>Neither agree nor disagree</th>
<th>Slightly agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. It is easy to prepare my Mic-Key button tubing for use each time a need it</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. It is messy to prepare my Mic-Key button tubing for use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. It is easy to insert my Mic-Key button tubing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I find inserting the Mic-Key button tubing is difficult sometimes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. The design of the Mic-Key button tubing makes it easy to insert</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. The Mic-Key button tubing is fiddly to use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. I feel confident in my ability to use my Mic-Key button</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convenience</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Storage of Mic-Key button tubing at home is inconvenient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Taking enough Mic-Key button tubing for a weekend away is very inconvenient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Taking enough Mic-Key button tubing for a 2-week holiday is very inconvenient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discreetness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. My Mic-Key button tubing is discreet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I can use my Mic-Key button tubing discreetly when I am away from home</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. My Mic-Key button tubing allows me to feel confident when away from home</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological well-being</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. I am self-conscious about my need to use my Mic-Key button</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. I would feel embarrassed if people saw my Mic-Key button tubing in my pocket</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. My need to use a Mic-Key button sometimes makes me feel embarrassed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. I worry that my Mic-Key button doesn't always empty my bladder fully</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. My need to use Mic-Key button tubing stops me from visiting friends and family as often as I would like</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. I worry about the risk of long-term problems from using my Mic-Key button</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Placement into an established tract

This technique is used for children with a pre-existing vesicostomy. In the operating room the vesicostomy tract is dilated to 18F and the vesicostomy button measuring device is used to choose the appropriate button size. The button is then placed directly into the vesicostomy tract and the balloon inflated.

After placement it is our practice to continue the button to constant drainage for 24-48 hours then began intermittent bladder drainage via the extension tubing. We change the button every 6-8 weeks in the office with a nurse or by the parent at home.

RESULTS

Thirteen children have had a vesicostomy button placed at our institution from 2011 to 2015, ages 7 months to 18 years with an average age of 5 years (median 3.8 years). Follow-up has been 24.75 months on average (range 3-54); only 2 patients do not have ongoing urology follow-up as one is followed solely by nephrology and the other has transitioned to adult urology care. Indications for placement included neurogenic bladder (5), non-neurogenic neurogenic bladder disorders (3), and valve bladders (5). Currently 10 children are still using the vesicostomy button while 2 children have had the button removed and are voiding spontaneously and 1 child was converted back to a traditional vesicostomy. All buttons were placed either because patient or family was unable to catheterize secondary to patient anatomy or patient was sensate and did not tolerate CIC. Table-1 shows the patient demographics.

Three patients with vesicostomy buttons were transplant recipients. All three children had a diagnosis of a posterior urethral valve. All three patients have normal sensation and had a vesicostomy performed soon after birth for valve and renal failure. Two of the three patients still have buttons in place. The third patient, an 11-years-old, had the button placed for assessment of bladder capacity and possible function as he had had a vesicostomy since birth. However, the patient’s creatinine rose after placement and he was not compliant with drainage schedule, he was converted back to a vesicostomy.

Postoperative complications (within 30 days) were minor including UTI (3), wound infection (1), and button malfunction (3). Button malfunction was considered a complication if the patient was seen in the emergency department or clinic for significant leakage requiring button or tubing change before the planned initial change or for dislodged buttons. Seven patients had the vesicostomy button placed through an existing vesicostomy track at time of vesicostomy revision. Five patients had the button placed via the endoscopic approach. One patient had an open vesicostomy button insertion. Five out of the seven patients (71%) with buttons placed into previous vesicostomy and the one patient (100%) who underwent open placement had leakage around the vesicostomy button. Conversely, none of the patients with the endoscopic approach had leakage.
To assess for upper tract deterioration creatinine and imaging were used if available. Creatinine was measured before and approximately 1 month after button placement in 10 patients. Creatinine remained stable in all 10 patients (maximum change = 0.12 mg/dL). The patient in which the button was removed for non-compliance and creatinine elevation occurred 3 months after placement, this elevation was concomitant with a UTI and resolved with vesicostomy button removal. Upper tract imaging was available in 12 patients. Ten renal ultrasounds confirmed absence of hydronephrosis or stable to improved hydronephrosis post-placement. The other two patients had nuclear medicine scans (MAG3 renal Lasix scan and DMSA) confirming equal and stable function bilaterally.

One patient in our series used the button for bladder cycling prior to successful transplantation.

Four children had recurrent UTI’s documented before insertion and continued to have infections after placement. Three additional children began experiencing UTI’s after placement.

Table 1 - Patient Demographics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Indications</th>
<th>Placement Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Neurogenic Bladder</td>
<td>Acute Retention, Unable to Tolerate CIC</td>
<td>Existing Vesicostomy</td>
</tr>
<tr>
<td>2</td>
<td>3.8</td>
<td>Valve Bladder</td>
<td>Unable to Tolerate CIC, Prior Vesicostomy</td>
<td>Existing Vesicostomy</td>
</tr>
<tr>
<td>3</td>
<td>0.6</td>
<td>Neurogenic Bladder</td>
<td>Parents Unwilling to Perform CIC</td>
<td>Endoscopic</td>
</tr>
<tr>
<td>4</td>
<td>4.8</td>
<td>Non-neurogenic Neurogenic Bladder</td>
<td>Unable to do CIC due to Anatomy</td>
<td>Endoscopic</td>
</tr>
<tr>
<td>5</td>
<td>1.6</td>
<td>Valve Bladder</td>
<td>Placed to Cycle Bladder Pre-transplant</td>
<td>Existing Vesicostomy</td>
</tr>
<tr>
<td>6</td>
<td>4.3</td>
<td>Valve Bladder</td>
<td>Parents Unwilling to Perform CIC</td>
<td>Endoscopic</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>Neurogenic Bladder</td>
<td>Unable to do CIC due to Anatomy</td>
<td>Existing Vesicostomy</td>
</tr>
<tr>
<td>8</td>
<td>5.6</td>
<td>Neurogenic Bladder</td>
<td>Parents Unwilling to Perform CIC</td>
<td>Open</td>
</tr>
<tr>
<td>9</td>
<td>5.6</td>
<td>Non-neurogenic Neurogenic Bladder</td>
<td>Patient Unable to Tolerate CIC</td>
<td>Existing Vesicostomy</td>
</tr>
<tr>
<td>10</td>
<td>18.3</td>
<td>Non-neurogenic Neurogenic Bladder</td>
<td>Patient Unable to Tolerate CIC, Prior Vesicostomy</td>
<td>Existing Vesicostomy</td>
</tr>
<tr>
<td>11</td>
<td>2.8</td>
<td>Valve Bladder</td>
<td>Acute Retention, Unable to Tolerate CIC</td>
<td>Endoscopic</td>
</tr>
<tr>
<td>12</td>
<td>11.6</td>
<td>Valve Bladder</td>
<td>Patient Unable to Tolerate CIC, Prior Vesicostomy</td>
<td>Existing Vesicostomy</td>
</tr>
<tr>
<td>13</td>
<td>3.1</td>
<td>Neurogenic Bladder</td>
<td>Cloacal Malformation, Patient Unable to tolerate CIC</td>
<td>Endoscopic</td>
</tr>
</tbody>
</table>
One child presented with erythema at the vesicostomy button site was diagnosed with a wound infection; this was treated with Keflex® for local cellulitis.

Three patients were reported to have button malfunction issues within their first 30 days after placement. These issues included leakage around the button ultimately requiring button revision (1), the button became dislodged requiring nursing replacement (1), and difficulty with the drainage tubing to the button (1) which was resolved with nurse teaching.

Eight vesicostomy patients and 6 CIC patients were compared in regards to QoL using the questionnaire. Mean age of vesicostomy button patient at time of survey was 6.6 compared to CIC group at age 7.3. Table-2 shows patient demographics for both groups.

Mean scores were evaluated for each domain and an overall QoL score as shown in Table-3. Figure-3 shows the mean scores for the cohorts in each domain. An overall QoL score included a total of 19 questions with the highest possible score of 95. The vesicostomy button cohort had an average score of 69.8 while the CIC cohort averaged 72.3 (p-value=0.65). Thus, there was no statistical difference in QoL when using the vesicostomy button versus CIC.

**DISCUSSION**

The vesicostomy button is an acceptable alternative to traditional vesicostomy or CIC. An important consideration in the use of the vesicostomy button is that it is a temporary measure to allow the child to achieve his/her voiding baseline and develop a definitive plan while keeping his/her upper tracts safe and bladder functioning with social continence. The 30 day morbidity of the button is quite low. Generally, the button is used as a bridge to a more definitive procedure or reconstruction. In our series, the average length of button placement was around 2 years. The plan for the majority of these patients is eventual reconstruction to achieve continence. However, some patients have been very happy with the button and do not desire reconstruction. Because the tube is a vesicostomy button and not a Foley catheter, there

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**Table 2 - Patient Demographics.**

<table>
<thead>
<tr>
<th>CIC Cohort</th>
<th>Vesicostomy Button Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
</tr>
</tbody>
</table>
is a maximum length of 5 cm and in one larger patient the button required removal because she had grown larger than the maximum offered length.

Urinary tract infections were a prominent finding throughout the study. We found that if the child had recurrent uti’s prior to button placement that this was likely to continue after placement.

Our leakage rate of 71-100% for those patients that had placement into an existing vesicostomy or open button placement was consistent with the findings described by Haider et al. (2). The leakage was significant in 2 patients (40%), these patients eventually required button revision. Endoscopic placement is superior in regards to achieving dryness post-operatively. Existing vesicostomy tract should be avoided if end goal of treatment is total dryness.

We found when reviewing our QoL surveys that the vesicostomy button is comparable to CIC, specifically in regards to ease of use, convenience, discreetness and psychological well-being. Vesicostomy is a good alternative to CIC when it cannot be tolerated due to patient anatomy or intact genital sensation.

To our knowledge, this is the first study to assess pediatric patients’ perceived quality of life while using alternate bladder emptying strategies. Mosiello et al. (7) studied their experience with cystotomy button in the pediatric population and found that it was well accepted by patients

<table>
<thead>
<tr>
<th>Table 3 - QoL Scores.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Overall QoL Score</td>
</tr>
<tr>
<td>Max = 95</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>72.3</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>69.75</td>
</tr>
<tr>
<td>p-value</td>
</tr>
<tr>
<td>0.65</td>
</tr>
<tr>
<td>Mean QoL Score (SD)</td>
</tr>
<tr>
<td>Max = 5</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>3.77 (1.47)</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>3.71 (1.48)</td>
</tr>
<tr>
<td>Overall Ease of Use Score</td>
</tr>
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<td>Max = 35</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>27</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>26.13</td>
</tr>
<tr>
<td>Mean Ease of Use Score (SD)</td>
</tr>
<tr>
<td>Max = 5</td>
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<tr>
<td>3.63 (0.51)</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>3.64 (0.99)</td>
</tr>
<tr>
<td>Overall Convenience Score</td>
</tr>
<tr>
<td>Max = 15</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>13.83</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>11.88</td>
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<tr>
<td>Mean Convenience Score (SD)</td>
</tr>
<tr>
<td>Max = 5</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>4.62 (0.66)</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>4.19 (0.92)</td>
</tr>
<tr>
<td>Overall Discreetness Score</td>
</tr>
<tr>
<td>Max = 15</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>10.38</td>
</tr>
<tr>
<td>Mean Discreetness Score (SD)</td>
</tr>
<tr>
<td>Max = 5</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>3.99 (0.83)</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>3.45 (0.69)</td>
</tr>
<tr>
<td>Overall Psychological Well-Being Score</td>
</tr>
<tr>
<td>Max = 30</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>19.5</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>21.38</td>
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<tr>
<td>Mean Psychological Well-Being Score (SD)</td>
</tr>
<tr>
<td>Max = 5</td>
</tr>
<tr>
<td>CIC Cohort</td>
</tr>
<tr>
<td>3.26 (1.01)</td>
</tr>
<tr>
<td>Vescicostomy Button Cohort</td>
</tr>
<tr>
<td>3.6 (0.73)</td>
</tr>
</tbody>
</table>

**Figure 3 - CIC versus vesicostomy QoL scores by domain.**

**QoL Scores by Domain**

![Graph showing QoL scores by domain](image)

![Graph showing QoL scores by domain](image)
and families. While they concluded that it could improve patient satisfaction and quality of life, no objective data was collected. We found both cohorts were satisfied with their quality of life, both had average Qol scores over 3 (3.77 for CIC cohort and 3.71 for vesicostomy button cohort). Satisfactory Qol is a score greater than 2.5 (6).

We look forward to the growing body of literature in regards to vesicostomy button placement and hope to identify those that would benefit the most from its use.

**CONCLUSIONS**

We conclude that the button does not decrease UTI’s in the child with a history of UTI’s prior to placement. We also found that endoscopic placement is the best option with the least amount of button leakage. Quality of life is reported as equally good among children doing CIC and using the vesicostomy button for bladder drainage.

**COMPLIANCE WITH ETHICAL STANDARDS**

IRB Approved Study.

**CONFLICT OF INTEREST**

None declared.

**REFERENCES**


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Antioxidant action of alpha lipoic acid on the testis and epididymis of diabetic rats: morphological, sperm and immunohistochemical evaluation

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ABSTRACT

Introduction: Chronic hyperglycemia is caused by diabetes mellitus-committed genital morphophysiology, and oxidative stress is one of the main factors involved in this process. Alpha lipoic acid (ALA) can prevent metabolic and morphological changes in diabetic individuals.

Objectives: In present study, we evaluated the effects of regular ALA consumption on the spermatogenesis and histoarchitecture in the male genital system of diabetic rats.

Materials and Methods: Thirty-two Wistar rats were divided into groups: Control (CG); Diabetic Control (DCG), receiving commercial diet; ALA Group (ALAG) and Diabetic ALA Group (DALAG), fed diets with added ALA (300 mg/Kg bw). The diabetic groups received a single injection of streptozotocin (60 mg/kg). After sixty days of the diet, the animals were euthanized, and semen, testis and epididymis samples were collected. A histomorphometric analysis was performed to determine the epithelial height, tubular and luminal diameter, tubular and luminal area of seminiferous tubules and each epididymal region. Sertoli cells were evidenced using the antivimentin antibody and were quantified. The results were statistically analyzed by the ANOVA test.

Results: At the end of the experiment, the DALAG glycemia was significantly lower than DCG. The histomorphometric parameters of the seminiferous and epididymal tubules did not show improvement in the DALAG. However, there was an improvement in the DALAG in terms of the concentration, motility and percentage of spermatic pathologies, as well as in the number of Sertoli cells (p<0.001).

Conclusions: The results demonstrated that supplementation with the ALA antioxidant retards testicular lesions and preserve the process of spermatogenesis in diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a globally-known metabolic disorder characterized by chronic hyperglycemia and triggering systemic complications, among them cardiovascular diseases, nephropathies, and neuropathies (1, 2). The increased oxidative stress due to excess
glucose in the body's circulation results in a higher production of reactive oxidative species (ROS) or free radicals (3).

Testicular morphological changes as a consequence of the hyperglycemic effect of DM have been documented (4). The effect of DM on endocrine control of spermatogenesis is that it alters sexual gonads and their morphology (5). Decreased seminiferous and epididymal tubules, alterations in sperm parameters, decrease in Sertoli cell index, and damage in epithelial morphology with depletion and apoptosis of germ cells are associated with the resulting spermatogenesis impairment of oxidative stress (6, 7). The damage in the vimentin filaments of Sertoli cells causes dissociation of germ cells allowing apoptosis, which may result in sperm alterations in type I diabetes (8, 9).

Alpha lipoic acid (ALA) is known as a potent natural antioxidant with promising therapeutic applications, capable of restoring endogenous antioxidants (vitamins C and E), chelating free metals, and repairing oxidized proteins (10). It is used in the prevention of chronic conditions associated with oxidative stress, such as aging, cardiovascular diseases, as well as diabetes and its complications (11). ALA has been associated with improvement in the quality of life because it attenuates the symptoms of neuropathic diabetic patients who are given daily oral doses of the antioxidant (12).

Supplementation with antioxidants has been fundamental to prevent oxidative damage triggering reproductive dysfunction (13) and reverse testicular changes (14). The antioxidant effect of ALA on diabetes has been observed to be reflected in the decrease in glycemia levels (15). Mohasseb et al. (13) observed a reduction of oxidative damage in restoring the activity of the enzymes superoxide dismutase and glutathione peroxidase when ALA associated with vitamin C and vitamin E was administered, resulting in the improvement of testicular morphology.

Known for its potential in regenerating other antioxidants like vitamin C and vitamin E (16), ALA has been suggested as a therapeutic resource in dietary supplementation, whether associated with a normal diet or isolated oral supplement (17), reducing the oxidative damage of diabetes. The objective of this study was to evaluate the antioxidant effect of alpha lipoic acid in rats with STZ-induced diabetes on chronic hyperglycemia and its potential protective effect on spermatogenic dysfunction and male infertility (4, 13, 18).

MATERIALS AND METHODS

Experimental Protocol

The procedure with animals was approved by the Statistical Committee for the Use of Animals of the Federal Fluminense University (protocol CEUA-UFF number 799/16). All procedures followed the norms of the National Research Council (US) Institute for Laboratory Animal Research. Adult male rats of the Rattus norvegicus albinus variety, also known as Wistar, were kept in individual cages in the experimental animal room with relatively humid environments of 21–23°C with 60% humidity, clear and dark cycle control, and water provided ad libitum.

Animals

Thirty-two rats (12 weeks of age and weighing 250g) were randomly divided (n=8/group) into: Control Group (CG) and Diabetic Control Group (DCG) had a casein-based diet; ALA Group (ALAG) and Diabetic ALA Group (DALAG) were supplemented with ALA at a dose of 300 mg/kg body weight mixed with mash commercial feed.

Streptozotocin treatment and induction of diabetes

Before receiving the experimental diets, 16 rats were separated and induced with diabetes with a single intraperitoneal injection of buffer (0.1 moL/L sodium citrate, pH 4.5) of streptozotocin (STZ, Sigma Aldrich S0130) at a dose of 60 mg/kg (19). Normal groups were given citrate buffers to be submitted to the same injection protocol. After 72 hours, diabetes was confirmed by the measurement of glycemic levels after a 5-hour fasting period, and animals that had plasma levels of 270 mg/dL or greater were considered in the experiment (13). The animals were divided to initiate treatment.
Experimental Diet

The experimental diet was prepared in the Laboratory of Experimental Nutrition (LabNe) of UFF. The control groups consumed pelleted commercial feed (Nuvilab®, Nuvital, Paraná, Brazil) (Table 1). ALAG and DALAG consumed rations supplemented with 4-6g/kg ALA ration: purified R-isomer (Sigma Aldrich 62320). The ingredients were weighed and homogenized with boiling water in a Hobart® industrial mixer (São Paulo, SP, Brazil). The obtained mass was transformed into pellets and dried in a ventilated oven (Fabbe-Primar® nº 171, São Paulo, SP, Brazil) at 60°C for 24 hours.

Glycemic Analysis

After confirmation of diabetes by STZ induction the weight and glycemias of all the animals was measured. Establishing the 5-hour fasting period, the blood was punctured through the caudal vein and analysed with the Accu-Check Performa (Glucometer®, Roche) glycometer (14) weekly until the end of the experiment.

Sperm Parameters

After 60 days of consumption, the rats were euthanized with ketamine (75 mg/kg) along with xylazine (10 mg/kg). Immediately after the sacrifice, both testes and epididymis were collected. The tail of the right epididymis was sectioned and washed with 1mL of powdered milk thinner (20). Then a drop of this solution, placed on a heated blade at 35°C, was covered with cover slip for evaluation of motility (percentage) and vigour (0-5). These parameters were observed through optical microscopy, following the protocol established by the Brazilian College of Animal Reproduction (21). Subsequently, the hyposmotic test was performed as proposed by Dell’Acqua et al. (22). Spermatozoa diluted in Kenney’s medium, (20) in a ratio of 1:100 in saline formalin, were taken to the Neubauer chamber to calculate the sperm concentration (million/mL). The spermatozoa were also evaluated for their morphology following the recommendation of Filler (23).

Histological Processing

The left testicles and epididymis were separated. The testes were cleaved transversally and the epididymis longitudinally for visualization of the epididymal regions (6). The samples were fixed in Bouin’s solution and then stored in 10% buffered formalin. All material was included in the standard paraffin technique and 5 μm thick sections were subsequently stained with hematoxylin and eosin for histopathological examination and by immunohistochemistry for vimentin detection.

Morphometric analysis of the seminiferous tubules and epididymal regions

Sections stained with hematoxylin and eosin, visualized on an optical microscope coupled to a digital camera, were obtained from analysis and quantification of the seminiferous tubules.

Table 1 - Food composition of experimental groups.

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humidity (max)</td>
<td>125 g/kg</td>
</tr>
<tr>
<td>Crude protein (min)</td>
<td>220 g/kg</td>
</tr>
<tr>
<td>Ethereal extract (min)</td>
<td>40 g/kg</td>
</tr>
<tr>
<td>Mineral Matter (max)</td>
<td>90 g/kg</td>
</tr>
<tr>
<td>Gross Fiber (max)</td>
<td>70 g/kg</td>
</tr>
<tr>
<td>Calcium (min- max)</td>
<td>10-14 g/kg</td>
</tr>
<tr>
<td>Phosphorus (min)</td>
<td>8 g/kg</td>
</tr>
<tr>
<td>Alpha Lipoic acid*</td>
<td>4 – 6 g/kg</td>
</tr>
<tr>
<td>Vitamin A (min)</td>
<td>13,000 IU</td>
</tr>
<tr>
<td>Sodium (min)</td>
<td>2.7 g/kg</td>
</tr>
<tr>
<td>Iron (min)</td>
<td>0.05 g/kg</td>
</tr>
<tr>
<td>Manganese (min)</td>
<td>0.06 g/kg</td>
</tr>
<tr>
<td>Zinc (min)</td>
<td>0.06 g/kg</td>
</tr>
<tr>
<td>Copper (min)</td>
<td>0.01 g/kg</td>
</tr>
<tr>
<td>Iodine (min)</td>
<td>0.002 g/kg</td>
</tr>
<tr>
<td>Selenium (min)</td>
<td>5 x 10-5 g/kg</td>
</tr>
<tr>
<td>Cobalt (min)</td>
<td>0.0015 g/kg</td>
</tr>
<tr>
<td>Fluorine (max)</td>
<td>0.08 g/kg</td>
</tr>
<tr>
<td>Lysine (min)</td>
<td>12 g/kg</td>
</tr>
<tr>
<td>Methionine (min)</td>
<td>4 g/kg</td>
</tr>
</tbody>
</table>

Composition for each kg of food (minimum and / or maximum quantities). The groups consumed pelleted commercial feed (Nuvilab®, Nuvital, Paraná, Brazil). Addition in Alpha Lipoic acid group and Diabetic Alpha Lipoic acid group.
and epididymal tubules. Fifty seminiferous tubules were captured after the selection of the most rounded tubules according to Leblond and Clermont’s criteria (24). From the epididymal tubules, 20 tubules from the head, body, tail were randomly captured. All images were scanned for total area (TA) and luminal area (LA) measurement, total (TD) and luminal diameter (LD), and epithelial height (EH), which were analysed using ImageJ® software (version 1.50g, National Institutes of Health, Bethesda, MD, USA).

**Histomorphometric Parameters**

The tubule area was verified by delimiting the tubule in the basal membrane (TA) and bypassing the seminiferous tubule spermatids (LA). The TD and LD were measured using the average of two perpendicular lines. The EH was evaluated by the mean of four measurements in the epithelium (25).

**Immunohistochemical Processing**

Immunolabeling for mapping Sertoli Cells with an anti-vimentin monoclonal antibody (mouse 1:100) (Clone v9, Dako) was associated with the EnVision FLEX development system using 4 μm thick histological slices on salinized slides. The cuts were submitted to the automated process of dewaxing, hydration, and antigenic recovery in a single step in the PTLink Dako PT100 equipment. Then, the cuts were circled by the DAKO S2002 hydrophobic pen to prevent the diluted antibody solution from flowing. Subsequently, the slides were dehydrated in alcohol with increasing concentrations and submitted to four xylol baths. The slides were assembled with ALLKIMIA Synthetic Canada Balm for further microscopic analysis.

**Evaluation of Sertoli Cells**

The intermediate filaments of the Sertoli cells were labelled with vimentin and counted by the Cell Counter plugin of the Image J program. The mean number of cells counted per tubule of each experimental group was calculated according to the method proposed by Corrêa et al. (25).

**Statistical analysis**

The results were statistically evaluated using the one-way ANOVA test associated with the Bonferroni multiple-comparison test in the GraphPad InStat® version 3.01 program. The graphs shown were performed on GraphPad Prism® version 5. The significance in all tests was set at the p<0.05 level.

**RESULTS**

**Glycemia**

To begin the experiment, the animals were induced with STZ and after 72 hours the increase in glycemia above 270 mg/dL determined the establishment of type 1 diabetes. At the end of 60 days, DCG presented significant elevation of hyperglycemia (P<0.001). Unlike DALAG, at week 8, hyperglycemia was not statistically significant compared to the beginning of the experiment. According to Table-2, the hyperglycemia presented at the 8th week by DCG was significantly higher than the glycemic increase presented by DALAG.

**Testicular Histomorphometry**

Observed in the STZ-induced groups, there was a marked decrease in tubular diameter, desquamation of germ cells, and agglomeration of cells in the tubular lumen (Figure-1). In the testicular histomorphometry of Table-2, the parameters showed tubular reduction of the diabetic groups compared to the control groups (P<0.001). The results showed that DALAG and DCG did not present significant differences between them.

**Epididymal Histomorphometry**

The groups induced by STZ presented a significant decrease compared to the control groups in the parameters of the total and luminal areas, including the total and luminal diameters (p<0.001) of all epididymal regions. There was no significant change in epididymal tubules between DALAG and DCG (Table-3).

**Sperm Evaluation**

According to Figure-2, the diabetic groups had lower means for concentration (Figure-2A), motility (Figure-2B), vigour (Figure-2C), and hyposmotic tests (Figure-2D). There was significant improvement in concentration and motility in the diabetic group supplemented with ALA as compared to the
Table 2 – Glycemia, biometric of the testes and epididymis and histomorphometric analysis of the seminiferous tubules.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CG</th>
<th>ALAG</th>
<th>DCG</th>
<th>DALAG</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycemia (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 72h</td>
<td>127.04±6.76</td>
<td>124.64±7.93</td>
<td>440.12±52.66</td>
<td>429.66±62.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Last Day</td>
<td>118.33±9.07</td>
<td>138.33±17.78</td>
<td>576.50±30.13</td>
<td>498.50±51.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicle weight (g)</td>
<td>1.77±0.11</td>
<td>1.81±0.15</td>
<td>1.62±0.41</td>
<td>1.39±0.34</td>
<td>0.0598</td>
</tr>
<tr>
<td>Epididymis weight (g)</td>
<td>1.03±0.08</td>
<td>1.31±0.33</td>
<td>0.57±0.33</td>
<td>0.62±0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Testicle + Epididymis Weight (g)</td>
<td>2.74±0.20</td>
<td>3.47±0.93</td>
<td>2.19±0.54</td>
<td>2.02±0.47</td>
<td>0.0003</td>
</tr>
<tr>
<td>Epithelial Height (µm)</td>
<td>59.09±7.75</td>
<td>58.61±3.61</td>
<td>23.44±2.41</td>
<td>24.64±2.54</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total diameter (µm)</td>
<td>340.77±18.06</td>
<td>318.35±9.24</td>
<td>114.60±27.15</td>
<td>127.47±26.22</td>
<td>0.0886</td>
</tr>
<tr>
<td>Luminal diameter (µm)</td>
<td>208.33±38.84</td>
<td>205.33±10.22</td>
<td>97.82±8.58</td>
<td>100.69±2.16</td>
<td>0.9054</td>
</tr>
<tr>
<td>Total area (µm²)</td>
<td>88.62±59.11</td>
<td>82.99±53.06</td>
<td>35.58±28.11</td>
<td>35.52±19.74</td>
<td>0.0001</td>
</tr>
<tr>
<td>Luminal area (µm²)</td>
<td>73.29±47.29</td>
<td>69.37±28.08</td>
<td>30.25±10.67</td>
<td>31.82±13.46</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data are presented as mean±s.d. Values obtained from ANOVA test. * = Statistically significant differences from GC; ** = Statistically significant differences from ALAG; # = Statistically significant differences from DCG. **CG** = Control Group; **ALAG** = ALA Group; **DCG** = Diabetic Control Group; **DALAG** = Diabetic ALA Group.

Figure 1 - Photomicrographs comparing normal and diabetic groups. The arrows point to the epithelial flaking resulting in the agglomeration of the cells in the tubular lumen in the diabetic groups.
Table 3 - Histomorphometric analysis of epididymal tubules - head, body and tail.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CG</th>
<th>ALAG</th>
<th>DCG</th>
<th>DALAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA (µm²)</td>
<td>$32.77 \times 10^3 \pm 16.29 \times 10^2$</td>
<td>$29.83 \times 10^3 \pm 20.03 \times 10^2$</td>
<td>$25.97 \times 10^3 \pm 27.30 \times 10^2$</td>
<td>$26.26 \times 10^3 \pm 22.22 \times 10^2$</td>
</tr>
<tr>
<td>LA (µm²)</td>
<td>$16.86 \times 10^3 \pm 33.47 \times 10^2$</td>
<td>$15.16 \times 10^3 \pm 34.87 \times 10^2$</td>
<td>$10.22 \times 10^3 \pm 28.75 \times 10^2$</td>
<td>$11.96 \times 10^3 \pm 15.31 \times 10^2$</td>
</tr>
<tr>
<td>TD (µm)</td>
<td>$209.58 \pm 21.64$</td>
<td>$201.73 \pm 25.20$</td>
<td>$174.03 \pm 19.63$</td>
<td>$180.17 \pm 8.94$</td>
</tr>
<tr>
<td>LD (µm)</td>
<td>$143.89 \pm 12.74$</td>
<td>$135.01 \pm 14.33$</td>
<td>$109.34 \pm 17.83$</td>
<td>$120.78 \pm 9.53$</td>
</tr>
<tr>
<td>EH (µm)</td>
<td>$32.15 \pm 5.76$</td>
<td>$30.91 \pm 6.75$</td>
<td>$30.49 \pm 2.90$</td>
<td>$28.34 \pm 2.35$</td>
</tr>
<tr>
<td>Corpus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA (µm²)</td>
<td>$99.98 \times 10^3 \pm 11.24 \times 10^1$</td>
<td>$95.53 \times 10^3 \pm 14.47 \times 10^1$</td>
<td>$74.95 \times 10^3 \pm 91.35 \times 10^2$</td>
<td>$70.36 \times 10^3 \pm 76.50 \times 10^2$</td>
</tr>
<tr>
<td>LA (µm²)</td>
<td>$76.91 \times 10^3 \pm 97.75 \times 10^2$</td>
<td>$74.59 \times 10^3 \pm 12.30 \times 10^3$</td>
<td>$53.42 \times 10^3 \pm 81.73 \times 10^2$</td>
<td>$49.81 \times 10^3 \pm 69.53 \times 10^2$</td>
</tr>
<tr>
<td>TD (µm)</td>
<td>$351.68 \pm 22.96$</td>
<td>$344.61 \pm 26.52$</td>
<td>$307.32 \pm 18.35$</td>
<td>$294.63 \pm 17.61$</td>
</tr>
<tr>
<td>LD (µm)</td>
<td>$307.77 \pm 20.80$</td>
<td>$300.78 \pm 25.11$</td>
<td>$255.37 \pm 19.24$</td>
<td>$244.28 \pm 19.62$</td>
</tr>
<tr>
<td>EH (µm)</td>
<td>$20.39 \pm 1.55$</td>
<td>$19.28 \pm 1.43$</td>
<td>$22.22 \pm 3.32$</td>
<td>$22.90 \pm 1.49$</td>
</tr>
<tr>
<td>Tail</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA (µm²)</td>
<td>$23.09 \times 10^4 \pm 42.66 \times 10^3$</td>
<td>$28.53 \times 10^4 \pm 51.23 \times 10^3$</td>
<td>$13.88 \times 10^4 \pm 34.60 \times 10^3$</td>
<td>$9.72 \times 10^4 \pm 31.84 \times 10^3$</td>
</tr>
<tr>
<td>LA (µm²)</td>
<td>$20.34 \times 10^4 \pm 40.28 \times 10^4$</td>
<td>$24.87 \times 10^4 \pm 61.19 \times 10^3$</td>
<td>$10.73 \times 10^4 \pm 34.14 \times 10^3$</td>
<td>$7.31 \times 10^4 \pm 32.85 \times 10^3$</td>
</tr>
<tr>
<td>TD (µm)</td>
<td>$525.39 \pm 46.25$</td>
<td>$577.24 \pm 65.18$</td>
<td>$397.08 \pm 71.87$</td>
<td>$339.85 \pm 60.18$</td>
</tr>
<tr>
<td>LD (µm)</td>
<td>$493.44 \pm 46.42$</td>
<td>$543.16 \pm 69.27$</td>
<td>$354.89 \pm 76.48$</td>
<td>$284.91 \pm 72.42$</td>
</tr>
<tr>
<td>EH (µm)</td>
<td>$13.99 \pm 1.46$</td>
<td>$14.12 \pm 2.74$</td>
<td>$21.41 \pm 3.15$</td>
<td>$25.95 \pm 3.42$</td>
</tr>
</tbody>
</table>

Data are presented as mean±s.d. Values obtained from ANOVA test. * = Statistically significant differences from CG; ** = Statistically significant differences from ALAG; *** = Statistically significant differences from DCG. CG = Control Group; ALAG = ALA Group; DCG = Diabetic Control Group; DALAG = Diabetic ALA Group; TA = Total area; LA = Luminal area; TD = Total diameter; LD = Luminal diameter; EH = Epithelial height.

control diabetic group (p<0.0001). The sperm pathologies (total head and tail) were present in most diabetic groups. For this parameter, the group supplemented with ALA presented lower pathologies than DCG (p<0.0001).

Sertoli Cell Count

Sertoli cells were evidenced by the immunohistochemical labelling of vimentin (Figure-3). The diabetic groups had lower numbers of cells than CG and ALAG. In the cell count by tubules (Figure-2F), the number of cells in DALAG was significantly higher compared to DCG (p <0.001).

DISCUSSION

The induction of DM by streptozotocin was efficient in establishing pathological lesions affecting spermatogenesis. Chronic hyperglycemia is the main cause of increased production of ROS that favours tissue oxidative damage and may lead to sexual dysfunction (18). Antioxidants are known to reduce such tissue damage, especially in the diabetic setting (11-14).

Induction of diabetes by streptozotocin was confirmed in diabetic groups (>270mg/dL). Hyperglycemia was evaluated throughout the experiment and, at the end of 8 weeks, the supplemented rats presented an attenuation of the serum level compared to the first glycemic measurement. The diabetic group supplemented with ALA had lower final hyperglycemia than the control diabetic group. This data agrees with Mohasseb et al. (13) that showed that oral administration of ALA in combination with ascorbic acid and tocopherol promoted attenuation of glucose after 60 days of experiment. Alpha lipoic acid has the ability to restore other antioxidants, such as ascorbic acid and tocopherol to allow hypoglycemic action in diabetes (18).

Histopathological changes were observed and evidenced in testicular histomorphometry in
diabetic groups after induction by streptozotocin caused by free radicals. Kaplanoglu et al. (19) submitted diabetic rats to the oral dose of vitamin E for 4 weeks and found that the testicular morphology altered by streptozotocin-induced diabetes did not improve and had satisfactory results with the association of green tea. Aguirre-Arias et al. (14), evaluating vitamin C alone, observed a reversal in the histological changes of the seminiferous tubules of diabetic rats supplemented for 63 days. Mohasseb et al. (13) evaluated glycemia reduction and protective effect on spermatogenic cells in diabetes-induced rats after oral administration of ALA associated with vitamins C and E. However, in our experiment, the alpha lipoic acid provided in the diet did not favour the improvement of testicular histomorphometric parameters.

Regarding epididymal regions, the histomorphometric analysis showed tubular decrease of all epididymal regions influenced by diabetes. Similar results were observed by Soudamani et al. (6), who reported changes in the different regions of the epididymis as a decrease in tubular and luminal diameter in diabetic rats. The oxidative stress of diabetes can inhibit steroidogenesis without modifying the gonadal histoarchitecture (26). The diet supplemented with ALA had no effect on epididymal morphology in the diabetic rats.

The damage of diabetes on sperm parameters is similar to previous studies (27). Alpha lipoic
acid administered under conditions of oxidative stress improved the motility and concentration of the diabetic group, possibly through interaction with other antioxidants. Aguirre-Arias et al. (14) observed that the antioxidant ascorbic acid was able to reverse testicular damage, but the restoration of sperm motility or fertility was insufficient. ALA is capable of improving viability and sperm motility, minimizing DNA damage by its ability to penetrate the Krebs cycle, aiding in the production of ATP (28). Studies indicate that the use of ALA restoring spermatological parameters disturbed by the use of industrial substances improves sperm quality in cases of high testicular temperature and increased oxidative stress from varicocele (29, 30).

The expression of vimentin is found in Sertoli cells associated with membrane integrity. Xu et al. (8) observed a decrease of Sertoli cells in diabetics. This data was confirmed by our study. The group of diabetic rats supplemented with the ALA antioxidant presented higher numbers of cells, suggesting its effectiveness in protecting and delaying the apoptosis of Sertoli cells. It seems reasonable to suppose that this positive action on the Sertoli cells directly influences the parameters of the sperm evaluation of the diabetic group treated with ALA, which could explain the improvement observed in all parameters analysed.

CONCLUSION

DM is a disease known worldwide for compromising reproductive physiology. Our results suggest that oral ALA supplementation attenuates the loss of Sertoli cells and improves the concentration and sperm motility affected by diabetes.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared.

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Mating with seminal vesicle-excised male can affect the uterus phospholipid fatty-acids composition during implantation in an experimental mouse model

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ABSTRACT

Purpose: No comprehensive information is available about uterus fatty acid (FA) change during implantation period and possible effects of the seminal vesicle secretion on it.

Materials and Methods: In this study, we evaluated FA composition of uterus phospholipids during the implantation period in intact and seminal vesicle-excised (SVX) mated female mice. Forty NMRI female mice were divided into control (mated with intact male) and seminal vesicle excised (SVX)-mated (mated with SVX-male) groups. The phospholipid fatty acids composition was monitored during the first five days of pregnancy using gas chromatography and also implantation rate was evaluated on fifth day of pregnancy.

Results: We found that levels of linoleic acid (LNA) and arachidonic acid (ARA) showed a decreasing trend from the first to the third day of pregnancy and then started to increase on the fourth day and peaked on the fifth day. In contrast, the level of saturated FA (SFA) increased on the second and third day of pregnancy compared to the first (p<0.05) and then decreased on the fourth and fifth. We also found that the seminal vesicle secretion could affect the levels of LNA, ARA, SFA, and PUFA in uterine phospholipids especially on second and third day. Moreover, there was a positive correlation between ARA level and implantation rate in control but not SVX-mated groups.

Conclusions: It can be concluded that several uterus FA that have important roles in early pregnancy could be affected by seminal vesicle secretion.

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INTRODUCTION

In addition to maintaining cell integrity, modulating cell-cell and cell-matrix interactions and signal transduction, cellular membrane is also a crucial source of various lipid mediators. The phospholipid fatty acids (FA) affect the membrane lipid matrix and consequently the mobility, conformation, and function of the membrane proteins (1). On the other hand, successful implantation of the embryo takes place during a specific period known as the window of implantation in which fusion of the blastocyst and uterus cells membranes is an important event. In support of this,
essential roles of lipid molecules in mice embryo invasion have been emphasized previously (2). Beneficial effects of various FA (especially polyunsaturated FA, PUFA) on embryo implantation, and maintenance of pregnancy have been also observed (3). Experimental studies have confirmed the importance of FA as energy source for endometrium decidualization which is a necessary step for implantation (4). It has also been suggested that biophysical properties of the uterus and blastocyst membranes, such as bulk lipid fluidity or phospholipid bilayer polarity change in favor of membrane fusion and consequently the embryo implantation (5).

Phospholipids as a main component of the biological membrane are involved in the production of prostaglandins (PG) and related compounds which have a role in inflammatory processes and immune-mediated responses (6). Roles of such compounds in female fertility have been widely described by previous studies [reviewed by Sugimoto et al. (7)]. Also, change in uterine FA has been considered important in maintaining early pregnancy (8). Since membrane FA of uterus cells are the main precursors of uterus PG (8) and there is a growing body of evidence about crucial roles of PG in embryo implantation, any change in FA composition of the uterus phospholipids during the implantation period may affect the implantation and consequently the pregnancy outcome.

Seminal fluid (SF) contains different molecules that interact with epithelial cells in the female reproductive tract and influence expression of various genes and immune system responses and thus prepare the endometrium for implantation (9). It has been demonstrated that in the female mice deprived of contact with the male SF, the fetal loss rate was higher (10). Moreover, it has been seen that SF can induce expression of PG related genes in swine and horse endometrial cell (11). It was reported that one of the mechanisms through which SF is involved in implantation and pregnancy is regulating PG amount in the female genital tract (12). So, uterus phospholipids FA as the main precursors of the PG production can be possibly affected following mating and insemination. However, there is no information available regarding insemination and SF effects on uterus FA.

There is no detailed information about uterus FA changes during the implantation period in mice which takes place in first five days after mating. Moreover, possible effects of the seminal vesicle secretion as the main part of SF on uterus remain to be clarified. To address these issues, we evaluated FA composition of uterus phospholipids during the implantation period in intact and seminal vesicle-excised (SVX) mated female mice.

**MATERIALS AND METHODS**

**Animals**

Forty female and 16 male adult albino Naval Medical Research Institute (NMRI) two-month-old mice were obtained from RAZI institute, Iran. The average weight of the animals was 20.5±3.4 g. Animals were housed under standard conditions of 25±2ºC temperature, 60–70% humidity with 12 hrs light/dark cycle and received food (standard pellet manufactured by RAZI institute, Iran), and water *ad libitum*. Fatty acid composition of the standard chow pellet is shown in Table-1. All animal procedures were approved by the Animal Ethical Committee of Tabriz University of Medical Sciences (code TBZMED.REC.1394.357).

After one week of adaptation, the male mice were randomly divided into normal (n=8) and excised seminal vesicle (n=8) groups. To exci-
se the seminal vesicle glands, the male mice were first anaesthetized with an IP injection of ketamine/xylazine solution, 0.1 mL per 10 g body weight [1 mL ketamine (100 mg mL⁻¹) + 0.5 mL of xylazine (20 mg mL⁻¹) + 8.5 mL of saline] and total bilateral removal of seminal vesicles was performed through the posterior abdominal wall. At three weeks after the operation, the female mice were randomly divided into two groups: 1) the control group (n=20) which was allowed to mate with intact male mice and 2) SVX-mated group (n=20) which was allowed to mate with male mice without seminal vesicle glands. For natural mating, three female mice were placed overnight in a separate cage with a male mouse with or without seminal vesicle glands depending on the type of group.

Observation of a vaginal plug (for control group) or spermatozoa in the vaginal smear (for the SVX-mated group) in next morning indicates day one of pregnancy. The pregnant mice of each group were sacrificed on days 1–5 of pregnancy (four mice for each day of pregnancy). The uterus was surgically removed from each sacrificed female and washed with phosphate buffered saline (PBS). To determine counts of the implantation sites, 0.1 mL of 1% Chicago blue (Sigma Chemical Co., St. Louis, MO) in saline was injected via a tail vein based on the previously described method (13). The blue bands on uterine horns were considered as implantation sites (Figure-1) and the number of implantation sites per uterus was considered as implantation rate.

Fatty acids analysis

The Bligh-Dyer method was used to extract total lipids from the uterine tissues (14). Briefly, tissue was crushed in MeOH/chloroform solution (2:1) and centrifuged. After centrifugation, the supernatant was collected in another tube, chloroform and distilled water were added and the contents were mixed vigorously. The tube was again centrifuged and chloroform part which now contained lipids was collected. The chloroform-lipid fraction was partially dried under nitrogen stream. Thin layer chromatography (TLC) was performed on silica gel plate to separate the phospholipids. In hexane/diethyl ether/glacial acetic acid (70:30:1) solvent system, phospholipids remain in spotting place. After separation, the phospholipid fraction was scraped in a glass tube containing the hexane/methanol solution and methylated tridecanoic acid (13:0, Sigma chemicals) as an internal standard. For esterification of the FA, methanol with acetyl chloride was used as described previously (Lepage and Roy 1986). Fatty acid methyl esters (FAME) were prepared using a one-step direct transesterification. The reaction included a nucleophilic attack of methoxy ion (–CH₃O–) to the esteric bonds of between fatty acids and alcohol (glycerol or sphingosine) at 100°C which led to methyl ester formation. After trans-esterification reaction, 5 mL K₂CO₃ was added to stop the reaction and separate organic and aqueous phases. FAME located in organic (hexane) phase were collected and the derivatized samples were then injected into a 60x0.25-mm×0.2μM Teknokroma TR CN100 capillary column (Spain) using a Buck Scientific model 610 gas chromatograph (SRI Instruments, Torrance, USA). The oven temperature was increased from 170–210°C at the rate of 1°C/min and then maintained stable for 45 minutes.
Helium was applied as the carrier gas and the detection was done by flame ionization detector. To determine the retention times of the known FA, standards from Sigma chemicals were injected. Following fatty acids as the main and detectable fatty acids of uterus phospholipid were evaluated: 16:0, 16:1, 18:0, 18:1, 18:2, 18:3, and 20:4. The levels of individual FA were expressed as percentage share of the total. It should be noted that the data for the control group were previously used in a parallel study to evaluate effect of omega-3 and -6 enriched diets (15).

**Statistical analysis**

Normal distribution of the data was confirmed by Skewness and Kurtosis tests. To compare the FA levels among various pregnancy days and groups the two-way ANOVA was applied. In the case with significant difference, Tukey’s test was performed as the follow up test. Also, homoscedasticity of the variances was confirmed by Levene’s test. The Pearson correlation test was employed to evaluate possible associations between FA levels and implantation rate (p-values <0.05 were considered significant). SPSS V.16 software was used for the statistical analysis.

**RESULTS**

The uterine weight and uterine/body weight ratio of the animals are shown in Table-2. In control group, the uterine weight and uterine/body weight ratio on day one of pregnancy were significantly higher than days two, three and four (p<0.05), but surprisingly these factors did not significantly differ between days one and five of pregnancy. Although wet uterine weight on day five was higher than day two (p<0.05). We observed almost a similar pattern of change in the uterine weight of the SVX-mated group. Although in this group, the uterine/body weight ratio in days four and five of pregnancy were higher than days two and three (p<0.05). Besides, the ratios in days four and five were significantly higher in the SVX-mated group compared to the control group (Table-2).

We applied two-way ANOVA to find out if there are significance differences across the two groups or preimplantation days. Our results sho-

| Table 2 - Animals and their wet uterine weight as well as uterine weight/body weight ratio on various pregnancy days in control (n=20) and seminal vesicle excised (SVX)-mated (n=20) groups. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Day 1           | Day 2           | Day 3           | Day 4           | Day 5           |
| **Control group** |                 |                 |                 |                 |                 |
| Body weight (gr) | 33.82±3.67      | 29.80±3.37      | 33.90±3.04      | 32.40±2.56      | 32.70±1.67      |
| Wet uterine weight (mg) | 142.25±26.66 | 70.25±22.06a | 89.00±12.73a | 88.33±22.68a | 115.00±30.47b |
| (Uterine weight/body weight ratio)×1000 | 4.27±1.14 | 2.41±0.90a | 2.54±0.19a | 2.72±0.43a | 3.49±0.75c |
| **SVX-mated group** |                 |                 |                 |                 |                 |
| Body weight (gr) | 31.97±1.62      | 30.97±0.38      | 30.22±0.94      | 32.50±3.54      | 29.90±3.94      |
| Wet uterine weight (mg) | 124.25±26.41 | 78.75±22.29a | 75.75±26.86a | 118.00±6.68a | 139.50±11.12b |
| (Uterine weight/body weight ratio)×1000 | 3.90±0.88 | 2.55±0.76a | 2.50±0.85a | 3.65±0.50a | 4.69±0.35b,c,d, $ |

Data are shown as Mean ± S.D; Levene's test confirmed homoscedasticity of variances and two-way ANOVA was used to evaluate interaction between groups and days. Significant difference (p<0.05) in comparison with a Day 1; b Day 2; c Day 3 and d Day 4

$ Significant difference in comparison with the control group.
wed that the levels of palmitoleic acid (16:1), stearic acid (18:0, STA), oleic acid (18:1, OLA) and linolenic acid (18:3) did not significantly change throughout this period (p>0.05, Table-3). However, levels of palmitic acid (16:0, PAM) were significantly lower on day five compared with days two and three of pregnancy (p<0.05).

We found that levels of linoleic acid (18:2, LNA) and arachidonic acid (20:4, ARA) and consequently PUFA showed a significant decrease from day one to day three of pregnancy. However, their levels increased on days 4 and 5 of pregnancy as these levels were significantly higher than days 2 and 3 of pregnancy (p<0.05). The levels of the omega-6 FA on day five were clearly higher compared to the second, third and fourth day of pregnancy (p<0.05). In sharp contrast, the level of saturated FA (SFA) indicated an increase on days two and three compared to day one (p<0.05) and then decreased on the fourth and fifth days of pregnancy. The SFA/PUFA ratio changed similarly but the PUFA levels changed exactly in inverse proportion to the ratio and SFA levels. We observed that the ratio was higher on day three than day one of pregnancy and then started to decrease from the fourth day and reached the lowest level on the fifth day of pregnancy in our experimental window (Table-3). The linolenic (18:3) level did not change significantly during the implantation period and just was statistically lower on day five than day one of pregnancy (p<0.05).

To find out possible effects of seminal vesicle secretion on phospholipid FA composition in uterus tissue of mice during the window of implantation, we compared the FA levels between control and SVX-mated groups (data presented in Table-3). Our results demonstrated that effect of seminal vesicle secretion on the composition of the FA was prominent mostly on the second and third day of pregnancy. The levels of LNA on day three were significantly higher in SVX-mated group compared to controls (p=0.047). We observed that the levels of ARA and PUFA on the second and third day, were significantly lower in control group compared to the SVX-mated group. In contrast, the levels of SFA and SFA/PUFA on those days were higher in control group than the SVX-mated group. Also, the PAM level was significantly higher in control group than the SVX-mated group on the second day of pregnancy (p=0.045). On the fifth day, only the level of ARA showed a significant difference between control and SVX-mated groups (p=0.043, Table-3).

The implantation rate on day five of pregnancy was significantly higher in control group in comparison with SVX-mated females (9.5±1.29 and 7.25±1.25, respectively; p=0.047). We also evaluated the possible correlation between implantation rate and uterine phospholipid FA levels on the fifth day of pregnancy and found positive correlations between implantation rate and ARA and PUFA levels in control group and not SVX-mated mice (Figure-2).

**DISCUSSION**

Our results showed that in control group LNA and ARA, as well as PUFA levels, tended to decrease from first to the third day of pregnancy. It is possible that this happens as a result of the initiation of inflammatory processes following the mating and semen contact with the uterus and consumption of LNA and ARA as the main precursor of PG synthesis (6). Following deposition of semen, inflammatory response has been reported previously in the uterine lumen (16). In accordance with this, we found that the levels of LNA and ARA on the second and third day in the control group were lower than the SVX-mated group; which implies the pivotal role of seminal vesicle secretion in mating-induced inflammation and consequently, uterus phospholipid FA composition. We also found that the levels of LNA and ARA started to increase on days four and five of the pregnancy. Such an increasing slope in the levels of LNA and ARA could increase the availability of PG precursors. In support of this hypothesis, a close association between FA change and PG biosynthesis in endometrium has been reported previously (17). ARA participates in series 2 PG production such as prostaglandin E2 (PGE2) and prostaglandin F2 (PGF2); increased levels of PGE2 and PGF2 has been observed on day five of pregnancy (18). Moreover, previous studies have found rising trends in the expression of enzymes involved in PG synthesis and action in the uterus
Table 3 - Fatty acids composition of uterine phospholipids during window of implantation (days 1 to 5 of pregnancy) in intact (control, n=20) and seminal vesicle excised (SVX)-mated (n=20) mice.

<table>
<thead>
<tr>
<th>Day</th>
<th>Control</th>
<th>SVX-mated</th>
<th>Control</th>
<th>SVX-mated</th>
<th>Control</th>
<th>SVX-mated</th>
<th>Control</th>
<th>SVX-mated</th>
<th>Control</th>
<th>SVX-mated</th>
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<tr>
<td></td>
<td>16:0 (%)</td>
<td>16:1 (%)</td>
<td>18:0 (%)</td>
<td>18:1 (%)</td>
<td>18:2 (%)</td>
<td>18:3 (%)</td>
<td>20:4 (%)</td>
<td>SFA (%)</td>
<td>MUFA (%)</td>
<td>PUFA (%)</td>
</tr>
<tr>
<td>1</td>
<td>25.2±4.72</td>
<td>3.52±0.76</td>
<td>24.7±4.58</td>
<td>21.40±2.26</td>
<td>11.45±2.76</td>
<td>1.85±0.46</td>
<td>12.00±2.63</td>
<td>49.96±2.91</td>
<td>24.93±1.93</td>
<td>25.31±2.59</td>
</tr>
<tr>
<td>2</td>
<td>25.9±5.46</td>
<td>3.17±0.48</td>
<td>23.15±4.04</td>
<td>22.62±4.93</td>
<td>10.7±2.91</td>
<td>1.77±0.33</td>
<td>12.68±2.29</td>
<td>49.08±1.44</td>
<td>25.79±5.24</td>
<td>25.15±4.06</td>
</tr>
<tr>
<td>3</td>
<td>27.8±4.44</td>
<td>3.47±1.03</td>
<td>27.0±3.47</td>
<td>24.81±3.46</td>
<td>7.49±0.76</td>
<td>1.88±0.17</td>
<td>7.54±2.43</td>
<td>54.82±1.82</td>
<td>28.28±3.11</td>
<td>25.15±4.06</td>
</tr>
<tr>
<td>4</td>
<td>21.56±2.21*</td>
<td>4.06±0.81</td>
<td>23.08±3.20</td>
<td>27.00±4.44</td>
<td>10.16±1.91</td>
<td>2.63±0.74</td>
<td>11.55±1.51</td>
<td>48.46±0.76</td>
<td>31.06±3.77</td>
<td>16.92±1.72</td>
</tr>
<tr>
<td>5</td>
<td>24.1±4.65</td>
<td>3.72±0.58</td>
<td>29.33±3.91</td>
<td>24.84±4.18</td>
<td>5.29±1.18*</td>
<td>2.46±0.58</td>
<td>4.95±2.99*</td>
<td>58.82±4.66</td>
<td>32.09±4.67</td>
<td>24.34±3.30*</td>
</tr>
</tbody>
</table>

Data are shown as Mean ± S.D; SFA = saturated fatty acids; MUFA = mono-unsaturated fatty acids; PUFA = poly-unsaturated fatty acids; SFA/UFA = ratio of saturated to unsaturated fatty acids; Levene's test confirmed homoscedasticity of variances and two-way ANOVA was used to evaluate interaction between groups and days; Significant difference (p<0.05) in comparison with *Day1, +Day2, #Day3, $Day4$ and * between the groups at same day.
of mice during the preimplantation period (19). Possible explanation for the observed increase in LNA and ARA levels on days four and five of pregnancy is the presence of an embryo. However, as a limitation of our study it should be mentioned that we evaluated whole uterus and for better clarification future studies should investigate implantation site alone rather than whole uterus. In contrast with LNA and ARA, the PAM and SFA level increased on days two and three and decreased on days four and five of pregnancy. Increase in PUFA and decrease in PAM and SFA levels in total uterine phospholipids on days four and five could possibly augment the membrane lipid fluidity. Since during implantation the membranes of blastocyst and uterus are fused together, such alterations might be in favor of embryo implantation (5). Another reason for reduction of PAM and SFA could be consumption as an energy source, since the importance of FA as an energy source for decidualization has been previously reported (4).

Comparison of the FA composition between the groups showed that LNA and ARA, as well as PUFA levels, were significantly higher and SFA level was lower on the second and third day of pregnancy in mice mated with SVX males compared to the control group. Presence of semen in the female reproductive tract, especially in mice where the semen directly comes in contact with the uterus, could induce inflammatory responses (20). It has been well documented that the immediate response to insemination in the mice is induction of proinflammatory cytokines synthesis in uterine epithelial cells, such as interleukin 6 and 8, macrophage chemotactic protein-1 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (21). Production of PG, especially series 2 is essential for promoting inflammation and their production depends on the supply of precursors such as LNA and ARA. Possible reason for the higher levels of LNA and ARA on days two and three in female mice mated with SVX male is a weaker post-coital inflammatory response in the female, and consequently less LNA and ARA depletion from the pool of membrane phospholipids. In accordance with this explanation, in our recent study we observed lower expression of enzymes responsible for PG biosynthesis in the uterus of mice mated with SVX male, compared to that of the control (12). In the present study, we found a higher level of ARA on implantation day in the uterus of the control group than the SVX-mated group. The increased level of ARA on the day of implantation possibly was observed due to the
presence of an embryo. Considering that a higher implantation rate was observed in control than the SVX-mated group, the higher ARA level in the control group could be due to higher implantation rate and embryo numbers.

As we also reported previously (15), there were positive correlations between levels of ARA and PUFA on the day of implantation with the implantation rate in normally mated group. In accordance with this findings, a higher amount of ARA in the uterus of pregnant cows than non-pregnant cows has been demonstrated previously (22). The observed association could be due to the important role of ARA as the precursor of PG which are essential for implantation through inducing angiogenesis and vascular permeability (23). We did not observe the same association in the SVX-mated group, which could be due to disruption of implantation time and/or signaling in this group. Also, increase in ARA and PUFA in the membrane of uterus cells can increase the membrane fluidity and so provoke cell signaling and membrane permeability which can potentially affect embryo-endometrial crosstalk through protein and exosomes/microvesicles mediated signaling during implantation (24). Induction of cell membrane fluidity following increase in PUFA and ARA levels could also affect the endometrial cell- matrix and cell-cell interactions which can potentially affect embryo apposition, adhesion, and invasion. The phospholipid fatty acids (FA) affect the membrane lipid matrix and consequently the mobility, conformation, and function of the membrane proteins (1). On the other hand, successful implantation of the embryo takes place during a specific period known as the window of implantation in which fusion of the blastocyst and uterus cells membranes is an important event. In support of this, essential roles of lipid molecules in mice embryo invasion have been emphasized previously (2).

However, our study was preliminary and it remained to be clarified how the changes in phospholipid FA in the uterus during implantation could play a role in implantation and pregnancy outcome. Besides, the present study evaluated effect of seminal vesicles secretion at implantation window and it needs to be investigated that if it can also affect the pregnancy at post-implantation level or not. Future study could be conducted on phospholipids changes during implantation and implantation period in different cells of the uterus as well as in implantation and non-implantation sites.

CONCLUSIONS

In conclusion, our results showed that the phospholipid FA composition, especially LNA and ARA levels were changed during the window of implantation in mice uterine tissue. Levels of these FA increased on the day of implantation, while the SFA level decreased. Also, we observed that the seminal vesicle secretion could possibly affect the levels of LNA, ARA, SFA, and PUFA in uterine phospholipids, especially on days 2 and 3 of pregnancy. Considering such changes in uterine FA composition during the implantation period, it could be concluded that FA, especially those participating in PG biosynthesis, may have an important role in early pregnancy. Moreover, seminal vesicle secretion could affect implantation process partly through affecting the uterine fatty acids composition.

ABBREVIATIONS

ARA = arachidonic acid
FA = fatty acid
LNA = linoleic acid
PG = prostaglandins
PGE2 = prostaglandin E2
PGF2α = prostaglandin F2α
SVX = seminal vesicle-excised
SFA = saturated fatty acid
SF = Seminal fluid
TLC = Thin layer chromatography

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CONFLICT OF INTEREST

None declared.

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Thyroid–like follicular carcinoma of the kidney presenting on a ten year–old prepubertal girl

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ABSTRACT

The very rare thyroid-like carcinoma of the kidney (TLCK) is microscopically similar to thyroid follicular cell carcinoma (TFCC). Differential diagnosis with secondary thyroid tumors depends on non-reactivity to immunohistochemical (IHC) markers for TFCC (thyroglobulin - TG and TTF1). We herein describe the fourth Pediatric case in literature and extensively review the subject. Only 29 cases were published to the moment. Most cases were asymptomatic and incidentally detected. Most tumors are hyperechoic and hyperdense with low grade heterogenous enhancement on CT and MRI. Most patients were treated with radical nephrectomy, but partial nephrectomy was used in some cases, apparently with the same results. Metastases are uncommon and apparently do not change prognosis, but follow-ups are limited. Up to the moment, TLCK presents as a low grade malignancy that may be treated exclusively with surgery and frequently with partial kidney renal preservation. A preoperative percutaneous biopsy is a common procedure to investigate atypical tumors in childhood and adult tumors. To recognize the possibility of TLCK is fundamental to avoid unnecessary thyroidectomies in those patients, supposing a primary thyroid tumor.

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INTRODUCTION

Thyroid–like carcinoma of the kidney (TLCK) is microscopically similar to thyroid follicular cell carcinoma (TFCC) and depends on non-reactivity to immunohistochemical (IHC) markers for TFCC (thyroglobulin-TG and TTF1) and on exclusion of other primary renal tumors for diagnosis. We describe a Pediatric case with a literature review.

CLINICAL SCENARIO AND RATIONAL

Clinical and pathologic findings
A 10 year–old pre-pubertal female presented with abdominal pain and occasional nausea and vomiting for two months. Her physical examination was normal. An abdominal ultrasound showed an encapsulated 82x69x42mm solid mass with mixed echogenicity, predominantly hype-
rechoic, in the medium/superior poles of the right kidney. A thoracoabdominal CT confirmed an exophytic, lobulated, solid, circumscribed 63x60x47mm mass in the superior and anterior medium third of the right kidney, with heterogeneous low enhancement after contrast injection. Necrotic and cystic areas were present, abutting but not invading the renal pelvis and hilar vessels. Augmented perihilar and pericaval lymph nodes were present (Figure-1). Her thyroid was functionally normal. No thyroid, ovarian, pelvic, cervical or thoracic tumors were demonstrated.

Right radical nephrectomy and locoregional lymphadenectomy were performed. The kidney mass measured 55x50x50mm and was well encapsulated, showing cystic and solid areas (Figure-1). Microscopically the main feature was the strong resemblance to thyroid tissue. At low magnification the tumor was composed of follicles of variable size. The follicles were lined by cuboidal or flattened epithelial cells and the material in the follicles was eosinophilic. The nuclei were round with uniform distribution of chromatin. Calcification, fibrosis, hemorrhage and necrosis were focally seen. The mass was restricted to the kidney, without vascular, adrenal, renal sinus or lymphatic invasion. The lymph nodes showed no metastases. Immunohistochemistry demonstrated non-reactivity for TTF-1 and thyroglobulin. The tumor cells were also non-immunoreactive with CK20, CD117 and RCC. Other markers were tested with positive results for PAX8, CK7, EMA and vimentin. After 1 year 7 months the patient persists asymptomatic with normal abdominal ultrasounds.

Figure 1 - Thyroid-like carcinoma of the kidney. (A) CT with contrast, showing heterogeneous low grade enhancement of the tumor. (B) Well defined tumor showing cystic, hemorrhagic and solid areas. (C) Follicular architecture with microfollicles and macrofollicles filled with colloid-like material.
DISCUSSION AND FUTURE PERSPECTIVES

Twenty-five cases of TLCK have been described. Another 4 are available in Chinese (n=3) and German (n=1). Females predominate (14 females, 6 males, 1 unknown). Ages vary between 19-83 years-old (mean 42.7, median 35). Females tended to be younger (median 32 versus 55 years-old for males). Only 3 other pediatric cases were published (5.3-14 years-old, 2/3 females) (1).

Most cases were asymptomatic, incidentally detected. Approximately 1/5 presented hematuria and/or flank pain. One patient each showed weight loss, anemia and hypertension (cured after resection of a perihilar tumor) (2). Many tumors were associated with previous malignancy (5/22) or pre-neoplastic conditions (1 case, adult polycystic renal disease).

TLCK predominates in the right kidney (14/22 cases, 63.6%), maximal dimensions varying between 11 and 118mm (mean 44.8mm). Four (18.2%), 11 (50%) and 7 (31.8%) affected the upper, mid and lower poles, respectively.

Most tumors were hyperechoic (contrasting with TFCC, usually hypoechoic) and hyperdense with low grade heterogenous enhancement on CT and MRI. On pre-contrast MRI TLCK showed high signal on T1 and low signal on T2, as compared to the kidney parenchyma (3). Some presented calcifications. No vascular or urothelial invasion were described, but vessels and renal calices might be displaced. Only two PET scan results are available, both positive to FDG marking (3, 4). Abdominal lymph nodes augmentation most commonly did not correspond to metastasis.

Most patients were treated with radical nephrectomy. Partial nephrectomy was used in 6 cases, apparently with the same results. Three patients presented lung metastases (3, 5). Curiously, in one case the metastatic nodule was immunoreactive to TTF1, as opposed to the kidney specimen (6). Three adults showed abdominal lymph node metastasis (5, 7).

Follow-up is limited (median 20 months). Most patients did not show progression of the disease or metastases (Table-1).

Differential diagnosis depends on IHC profile. The diseases to be considered are:

1. Malignancies:
   a. Renal metastasis from TFCC from normal or ectopic thyroid tissue (possible on the neck and/or thorax, mainly in the vicinity of the thyroid gland, but not in kidney tissue (6)). Less than 40 cases were described (4), generally associated with widespread metastatic disease (mostly to the lungs, lymph nodes and bones). The metastases are positive to TTF1/TG. A primary tumor should be detectable.
   b. Metastasis from struma ovarii (2% of the ovarian tumors, malignant in 5-10% of the cases). Metastases are rare (5%), preferentially to the liver and peritoneum, and positive to TTF1/TG (6).
   c. Papillary renal cell carcinoma may show patchy “thyroid-like” areas, but the typical architecture usually predominates. IHC is positive to kidney tumor markers.
   d. Renal carcinoids may show zonal “follicular” architecture, positive to neuroendocrine markers (synaptophysin, CD 56 and chromogranin). Oncocytomas and metanephric adenomas may also show focal or patchy “follicular” architecture, due to eosinophilic intraluminal deposits in areas of tubular differentiation.

2. Benign entities:
   a. Kidney “thyreodization” associated to end-stage kidney disease/pyelonephritis, caused by the deposit of colloid-like protein material in the lumina of atrophic distal tubules/collection ducts. This is a diffuse and bilateral process, not associated with tumors.

TLCK are well circumscribed, yellow/whitish. Hemorrhagic and necrotic areas are common and may present as intratumoral “cysts” (2, 8, 9).
Table 1 - Summary of clinical characteristics of the tumors described in the literature plus present case.

<table>
<thead>
<tr>
<th>Author/publication year</th>
<th>Age (years)/sex</th>
<th>Presentation</th>
<th>Past history</th>
<th>Local/size (mm)</th>
<th>Imaging</th>
<th>Nephrectomy (T/P)/FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessandrini, 2012</td>
<td>76 M</td>
<td>Hematuria</td>
<td>Prostate cancer</td>
<td>L UP, 50</td>
<td>(CT) Hyperdense, well vascularized, necrotic center, extension to adipose tissue, enlarged lymph nodes (no metastases).</td>
<td>T/ 11 months NED</td>
</tr>
<tr>
<td></td>
<td>41 F</td>
<td>Incidental</td>
<td>Hodgkin lymphoma</td>
<td>R LP, 50</td>
<td>(CT) complex cystic, hyperdense no enhancement. (MRI) solid septa</td>
<td>P/ 4 months NED</td>
</tr>
<tr>
<td>Muscara 2017 (12)</td>
<td>27 M</td>
<td>Incidental</td>
<td>-</td>
<td>Left UP, 65</td>
<td>-</td>
<td>P/8 months NED</td>
</tr>
<tr>
<td>Amin 2009 (7)</td>
<td>N=6 (29-83), 3M 3 F</td>
<td>All incidental</td>
<td>1 Colon cancer, 1 osteosarcoma</td>
<td>5R 1L / 4 MP, 2 LP/19-40</td>
<td>-</td>
<td>6 T/ 7-84 months, NED</td>
</tr>
<tr>
<td>Dawane 2015 (17)</td>
<td>49 F</td>
<td>Incidental</td>
<td>-</td>
<td>L MP 24</td>
<td>(CT) contrast enhancement, extension to adipose tissue.</td>
<td>P/ 5 years, NED</td>
</tr>
<tr>
<td>Khoja 2014 (18)</td>
<td>31 F</td>
<td>Hematuria, weight loss, flank pain (3 years), anemia</td>
<td>Normal thyroid (I/F), normal ovaries (I)</td>
<td>L UP 43</td>
<td>(CT) heterogeneous enhancing, distorting collecting system, lymph node enlargement (no metastases).</td>
<td>T/ 21 months NED</td>
</tr>
<tr>
<td>Jung 2006 (13)</td>
<td>32 F</td>
<td>Incidental</td>
<td>Normal thyroid (I/F), normal ovaries (I)</td>
<td>R LP/ 118</td>
<td>(CT) contrast enhancing, hydronephrosis.</td>
<td>T/ 6 months NED</td>
</tr>
<tr>
<td>Reference</td>
<td>Age</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Initial Imaging Findings</td>
<td>Follow Up</td>
<td></td>
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<tr>
<td>Dhillon 2011 (5)</td>
<td>34</td>
<td>F</td>
<td>Hematuria, flank pain</td>
<td>Normal thyroid (I/F)</td>
<td>R MP/63</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple pulmonary</td>
<td>“systemic</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>nodules (biopsy</td>
<td>treatment” for</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>“thyroid</td>
<td>thyroid cancer</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>carcinoma”)</td>
<td>(1 year)</td>
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<td></td>
<td></td>
<td></td>
<td>+ T nephrectomy/3 months NED</td>
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<tr>
<td>Lin 2014 (8)</td>
<td>65</td>
<td>M</td>
<td>Hematuria (4 years), back pain (1 week)</td>
<td>Normal thyroid (I/F)</td>
<td>R MP, 80</td>
<td></td>
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<td></td>
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<td>Hypoechoic hilar mass, (CT) “renal carcinoma”, normal fascia/ lymph nodes.</td>
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<td></td>
<td>T/ 2 years NED</td>
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<tr>
<td></td>
<td>59</td>
<td>F</td>
<td>Incidental</td>
<td>Normal thyroid (I/F)</td>
<td>R MP, 60</td>
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<td></td>
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<td></td>
<td></td>
<td>Normal fascia/ lymph nodes.</td>
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<td></td>
<td></td>
<td>T/ 1 month NED</td>
<td></td>
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<tr>
<td>Wu 2014 (4)</td>
<td>19</td>
<td>F</td>
<td>Incidental</td>
<td>Leukemia (5 years-old)</td>
<td>R LP 28</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(CT) heterogeneous</td>
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<td></td>
<td>hyperdense. No lymph nodes. No metastasis. PET (+).</td>
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<tr>
<td>Wang 2017 (2)</td>
<td>25</td>
<td>F</td>
<td>Severe hypertension (normal post-operative)</td>
<td>Normal thyroid (I/F), normal ovaries (I)</td>
<td>R MP 30</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(CT) inhomogenous</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>enhancement, calcifications. Ovaries normal (imaging).</td>
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<td></td>
<td></td>
<td></td>
<td>P/ 2 years NED.</td>
<td></td>
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<tr>
<td>Ghaouti 2014 (10)</td>
<td>68</td>
<td>F</td>
<td>Incidental</td>
<td>Normal thyroid (I/F), normal ovaries (I)</td>
<td>R MP 11</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(MRI) Cystic, no</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>enhancement.</td>
<td>P/ no FU reported</td>
<td></td>
</tr>
<tr>
<td>Volavsek 2013 (11)</td>
<td>34</td>
<td>?</td>
<td>Incidental</td>
<td>Nephrolithiasis, polycystic disease, adult type.</td>
<td>L LP 50 mm</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperechoic cyst</td>
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<td></td>
<td></td>
<td>T/ 6 months NED.</td>
<td></td>
</tr>
<tr>
<td>Sterfacci 2008 (6)</td>
<td>28</td>
<td>F</td>
<td>Incidental</td>
<td>L MP 44</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(CT) Heterogeneous, no capsule infiltration, displacement of blood vessels. Left lung nodule.</td>
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<td></td>
<td></td>
<td></td>
<td>Thyroidectomy</td>
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<td></td>
<td></td>
<td>(presumed metastatic thyroid cancer, despite normal imaging). Lung lumpectomy. T nephrectomy/5 years NED.</td>
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</tr>
</tbody>
</table>
Vicens 2014 (3) 24 F Hematuria, flank pain R MP, 60 (CT) displaying calices, bilobulated, peripheral calcification, hyperdense, low grade enhancement, peak on delayed phase. Multiple pulmonary nodules, enlarged abdominal lymphonodes. (MRI) increased signal T1, low signal T2, low grade enhancement. PET scan: mild FDG uptake. T/post op therapy with sunitinib for lung metastases. No FU data.

Malde 2013 (19) 29 F Flank pain Thyroid normal (F) L LP, 58 (CT) Complex multiseptated partially cystic, low attenuation, no enhancement. (MRI) no enhancement. T. No FU data.

Our case 10 F Flank pain, nausea, vomiting Thyroid (I/F) and ovaries I) normal R +SP/MP, 63 US hyperchoic heterogeneous, CT exophytic anterior superior/medium pole, heterogeneous enhancement, necrotic and cystic areas, lymph node enhancement (no metastases) T. NED, normal imaging after 19 months.

NED = no evidence of disease; FU = follow up; F = female; M = male; Fu = function; I = imaging; UP = upper pole; MP = mid pole; LP = lower pole; L = left; R = right; T = total; P = partial
Histologically there are macro and microfollicles filled with amorphous eosinophilic colloid-like material (5, 10), similar to TFCC. The follicles are lined with cuboidal cells with scant eosinophilic cytoplasm, round/oval nuclei and evenly distributed chromatin. Mitotic activity is absent or scarce. There may be focal areas of papillary differentiation, patchy lymphoid aggregates, calcifications (2, 3, 10-12) and cholesterol crystals (12). Fibrous septa presenting muscle and a fibrous pseudocapsule have been described (7, 12). No cases presented with vascular or collecting system invasion. Capsular invasion was seen in two cases (11).

The tumor is, by definition, negative to TG/TTF1, positive to epithelial markers (cytokeratins AE1/AE3, 7, PAX 2 and 8, Vimentin and EMA) and negative to renal tumor markers (WT1, RCC, CD10).

TLCK was described in 2006 (13), is an emerging entity and has not yet been included in the WHO classification of tumors (14). A possible previous case was positive for thyroid IHC markers (15) and is questionable. The predominance of young women suggests some hormonal influence and the relatively high incidence of previous malignancies suggests that previous treatments and/or specific genetic constitutions predispose to TLCK.

Extra-renal extra-thyroid tumors (cholangiocarcinoma, breast and urothelial carcinomas, endolymphatic sac tumor, plasmacytoma, papillary renal cell carcinoma) may also present “follicular” architecture and are negative for TG and TTF1 (4, 7, 16). Tubular deposits of Tamm-Horsfall glicoprotein are probably the explanation for the colloidal aspect in kidney tumors, including TLCK (5, 10).

Primary thyroid tumors are positive to TTF1/TG, except for poorly differentiated or sarcoma-like malignancies. For kidney tumors, the IHC panel includes vimentin, CK 7, AMACR, CCR and CD10 and WT1 in atypical tumors or children. A "thyroid tumor" on a kidney specimen is unexpected and at least one patient was, quite understandably, submitted to a thyroidectomy with the presumed diagnosis of metastatic TFCC, despite normal thyroid imaging (6). Non-reactivity to TG/TTF1 and no primary tumor are the clues to avoid this. Table-2 summarizes the IHC profiles and differential diagnosis for TFCC, kidney tumors and TLCK.

Surgical resection with clear margins is probably curative, despite the limitations of follow-up data. Partial nephrectomy seems to be as successful as total nephrectomy, but the high proportion of mid pole tumors may impose technical difficulties. Metastases are rare and apparently do not compromise the results in most patients. Adjuvant therapy has not been established.

**ACKNOWLEDGEMENT**

We would like to thank Dra. Therezinha C Fonseca de Sá and Dr. Paulo Faria, National Institute of Cancer, Ministry of Health, Rio de Janeiro, Brazil, for their invaluable help with the histological and immunohistochemical diagnosis of the patient, including the microphotographies and immunohistochemical panels shown in this research. This paper would not be possible without their assistance.
<table>
<thead>
<tr>
<th>Tumor</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC (Clear cell)</td>
<td>Vimentin</td>
<td>HMWCK</td>
</tr>
<tr>
<td></td>
<td>AE1/AE3</td>
<td>CK7, CK20</td>
</tr>
<tr>
<td></td>
<td>RCCM</td>
<td>e-cadherin,</td>
</tr>
<tr>
<td></td>
<td>PAX2/PAX8</td>
<td>CD117</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMACR</td>
</tr>
<tr>
<td>RCC (papillary)</td>
<td>Vimentin</td>
<td>CD117</td>
</tr>
<tr>
<td></td>
<td>AE1/AE3</td>
<td>CK7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMACR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCCM</td>
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<tr>
<td></td>
<td></td>
<td>PAX2/PAX8</td>
</tr>
<tr>
<td>Chromophobe RCC/oncocytoma</td>
<td>e-cadherin</td>
<td>Vimentin</td>
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CONFLICT OF INTEREST

None declared.

REFERENCES


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Synchronous presentation of muscle-invasive urothelial carcinoma of bladder and peritoneal malign mesothelioma

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ABSTRACT

Introduction: Cancer is one of the most important leading cause of death in man and woman in the world. The occurrence of new cancer has become more frequent in recent years due to strict screening protocols and occupational and environmental exposure to carcinogens. The incidence of secondary malignancies has also increased due to close medical follow-up and advanced age. Herein, we report a case and its management diagnosed as synchronous peritoneal malignant mesothelioma and muscle-invasive urothelial carcinoma.

Case Description: A 71-year-old male presented with macroscopic hematuria and abdominal distension increasing gradually. A contrast enhanced computerized tomography demonstrated bladder mass and diffuse ascites with nodular peritoneal thickening and umbilical mass. He was treated with the multidisciplinary team working including urologist, medical oncologist and general surgeon.

Conclusions: To our knowledge, this is the first case of peritoneal malign mesothelioma with synchronous muscle-invasive urothelial carcinoma. Because of the rarity of this condition, there is still no consensus on the definitive treatment protocols, yet. Individualized treatment with multidisciplinary close follow-up might improve the survival outcomes.

INTRODUCTION

Malign mesothelioma is a relatively rare cancer that arises from mesothelial cells of pleura, peritoneum, pericardium, and tunica vaginalis. Primary peritoneal mesothelioma (PM) accounts for 10% to 30% of all cases of malignant mesothelioma (1). Even though asbestos exposure plays an important role in the development of tumor cells, PM is rarely associated with asbestos exposure and tends to present at the younger age (2, 3). On the other hand, bladder cancer is one of the most common urologic malignancies. It was the 4th and 12th most frequent malignant tumor among men and women, respectively (4). Transitional cell cancer of bladder is the most common form and it accounts for about 90% of cases (5). Advanced age and smoking are identified as the most important independent risk factors for the development of this tumor. Although the incidence of the secondary malignancy in patients who have bladder cancer increase with the advanced age and longer follow-up, invasive urothelial carcinoma and synchronous malignant PM is a very
rare entity at the current literature. In this case, we aim to report this unusual case of muscle-invasive bladder cancer with synchronous peritoneal malign mesothelioma and discuss its management and treatment alternatives.

**CASE DESCRIPTION**

A seventy-one-year-old male patient without any history of asbestos exposure has admitted to our hospital with complaints of macroscopic hematuria and abdominal distension increasing gradually. In his medical history, he underwent transurethral resection of the prostate due to benign enlargement 5 years ago. Physical examination revealed abdominal distention with flank and shifting dullness. An umbilical nodule was also noted. The urinalysis revealed pyuria and microscopic hematuria, but the urine culture was sterile. An abdominal ultrasonography showed bladder mass measured as 15mm and diffuse intra-abdominal free fluid collection. A computerized tomography (CT) demonstrated diffuse ascites with nodular peritoneal thickening and multiple lymph nodes over 10mm at the internal iliac, common iliac and paraaortic regions. An umbilical mass measured as 30mm was also seen on CT imaging (Figure-1). Surgical treatment in the same session was desired by the patient. After written informed consent was obtained, a transurethral bladder tumor resection and laparoscopic peritoneectomy were carried out consisting of the omentum, left and right hemidiaphragm, pelvic peritoneum and umbilical mass. Pathologic examination revealed high-grade urothelial carcinoma with the muscularis propria invasion on the TUR specimen and malign PM on the peritoneal specimens. Immunohistochemistry was used to confirm pathologic diagnoses for both cancers. Immunohistochemically, urothelial carcinoma was widely positively stained with GATA and a focal positive with uroplakin III but no mesothelioma cells were stained. Additionally, mesothelioma cells were strongly and diffusely stained with calretinin, however, urothelial carcinoma cells were not stained (Figure-2). Sixth cycles of pemetrexed, cisplatin,

![Figure 1 - A) Peritoneal thickening on the right hemidiaphragm (black arrow). B) Diffuse omental invasion of peritoneal mesothelioma (omental caking, white arrow). C) CT imaging of umbilical mass (white arrow) D) Bladder mass with sessile growth pattern (white arrow).](image-url)
bevacizumab every three weeks were chosen for systemic chemotherapy for the treatment of both cancers. Patient tolerated well systemic chemotherapy and a CT scan showed no evidence of disease progression at the sixth months follow-up visit. After the interview with the patient about treatment options, hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin and doxorubicine was planned for peritoneal malignant mesothelioma. He is still monitored closely by the multidisciplinary team consisting of the urologist, medical oncologist, and general surgeon.

**DISCUSSION**

Peritoneal mesothelioma is a rare variant of malignant mesotheliomas. The prognosis depends primarily on the type of tumor. Localized and well-differentiated PM tends to be clinically indolent with survival in the range of years and even decades. However, diffuse and high-grade tumors are more destructive and infiltrative with a median survival time of less than 1 year (6). Several histologic parameters have been identified as predictors of worse prognosis. These are depth of invasion, mitotic count, nuclear grade, sarcomatoid differentiation, desmoplastic and lymphoid response, and lymph node metastasis (7). Although systemic chemotherapy has historically been the treatment of choice, there is still no certain consensus about optimal treatment of PM due to lack of comparative and high-quality studies.

Treatment alternatives for PM include observation, chemotherapy alone, cytoreductive surgery (CRS) alone, CRS combined with chemotherapy and CRS combined with HIPEC. One of the largest studies by Verma et al. suggested that combined modalities such as CRS/chemo and CRS/HIPEC had the most favorable results in terms of overall survival rates (8). On the contrary, treatment of muscle-invasive bladder cancer is well known at present. Definitive treatments are radical cystectomy with suitable urinary diversion and external beam radiation therapy for the organ-confined disease. Bladder-sparing modalities with trimodality therapy consisting of deep transurethral resection of bladder tumor combined with chemo and radiotherapy can be also considered in selected cases. Systemic chemotherapy with platinum-based regimes remains the first-line treatment for the advanced bladder cancer (9). In the presented case, we were not willing to perform radical cystectomy due to synchronous diagnose of PM.

Synchronous primary cancer with peritoneal malignant mesothelioma is an extremely rare condition. There are only a few reports related to this topic in the current literature. Jacobsen et al. reported a case of PM in a patient with non-muscle invasive urothelial carcinoma (10). The other published case reports only consist of gynecologic cancers (11). One of the largest studies by Atte-noos et al. reported that incidence of secondary malignancy after malignant mesothelioma as 1-2% at post-mortem examination. However, none of these were urogenital tumors (12). Additionally, Chen et al. reported that the incidence of renal cell carcinoma has increased in patients with malignant mesothelioma. But they didn’t declare any significant etiologic and genetic association among these tumors (13). On the other hand, the most frequent secondary malignancies after bladder cancer were
as follows: lung, prostate and breast cancer (14). Increased risk of secondary tumors may be attributable due to smoking and close medical follow-up after primary diagnose of the bladder tumor.

In conclusion, to our knowledge, this is the first case published in the literature who have muscle-invasive bladder cancer with synchronous peritoneal malign mesothelioma. As in the presented case, precise pathologic examination with correct immunohistochemical staining is essential to confirm the diagnosis and exclude other types of malignancies. In addition, accurate clinical staging of these tumors is needed in order to plan treatment options. However, no curative or definitive treatment is determined at the current literature since its extremely rare condition. Such challenging cases must be addressed through direct communication in a multidisciplinary tumor board setting. Individualized treatment with multidisciplinary close follow-up schemes might improve the survival outcomes in these patients.

CONFLICT OF INTEREST

None declared.

REFERENCES


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ABSTRACT

Testicular germ cell tumor is the most common cancer in 20-to 35-years-old men. There are known risk factors such as undescended testicle(s) and history of testicular cancer. Most lesions are germ cell tumors with two main subtypes: seminomas and non-seminomatous germ cell tumors.

INTRODUCTION

Testicular germ cell tumor is the most common cancer in 20-to 35-years-old men. There are known risk factors such as undescended testicle(s) and history of testicular cancer. Most lesions are germ cell tumors with two main subtypes: seminomas and non-seminomatous germ cell tumors. Burned out testicular tumor (BOTT) refers to a histological fibrous regression of the primary testicular lesion that generally presents at the stage of metastases (1). This case series shows imaging findings in three men with an atypical presentation of this malignancy, gas-containing retroperitoneal mass revealing in each case a BOTT. To our knowledge, this gas-containing mass has just been illustrated once (2).

CASE PRESENTATIONS

Case 1 - The first patient, a 57-years-old Caucasian man, came to the hospital with afebrile abdominal pain. Physical examination was normal. The biology laboratory results showed slight leukocytosis. Urine culture was sterile. Considering the abdominal pain with leukocytosis, we performed a contrast-enhanced CT-scan. The CT-scan showed a retroperitoneal hypodense mass containing gas (Figure-1A). There was no vascular thrombosis. At first, our diagnostic hypothesis was an abscess. However, there wasn’t any argument for an associated infection such as pyelonephritis, diverticulitis or spondylitis: there was no focal nephritis, bowel fistula or bone abnormalities.

Given a medical history of bilateral undescended testicles treated by orchidopexy in childhood, we carried out a testicular ultrasound (US) showing bilateral testicular atrophy, microlithiasis, and hypoechoic areas involving the left testis (Figure-2A). Nevertheless, the scrotal examination was normal. On the other hand, tumor markers including lactate dehydrogenase, alpha-fetoprotein and human chorionic gonadotropin levels were normal.

The patient underwent radical orchiectomy of the left testis and a seminoma with burned out main component was diagnosed. Finally, the patient underwent a fine needle biopsy of the mass revealing ischemic necrosis without any tumor cell.

Case 2 - The second patient, a 41-years-old Caucasian man, came to the hospital for the same reason, afebrile abdominal pain. Physical examination was also normal. The laboratory results showed slight leukocytosis and...
urine culture was sterile. In the same way, a contrast-enhanced CT-scan was performed and showed the same results: necrotic retroperitoneal mass containing gas (Figure-1B). The scrotal US revealed a diffuse hypoechoic aspect of the left testis compared to the contralateral testis. Tumors markers were normal.

Radical orchiectomy was performed and pathological examination found hyaline fibrosis without any tumor cell consistent with BOTT (Figure-2B). The CT guided biopsy of the retroperitoneal mass revealed a necrotic seminoma.

Case 3 - The third patient, a 34-years-old Caucasian man came to the hospital with afebrile lumbar pains and presented similar physical examination (including scrotal examination) and laboratory results.

The contrast-enhanced CT-scan also revealed a gas-containing retroperitoneal mass (Figure 1C). The scrotal US showed a hypoechoic hypovascular area with microlithiasis in the left testis (Figure-2C). Tumor markers were normal. The patient underwent a mass CT guided biopsy and an orchiectomy. The pathological analysis showed respectively necrosis and hyaline fibrosis without tumoral cells. Considering these results, we performed a second biopsy of the retroperitoneal mass that allowed to diagnose lymph node metastasis of a BOTT (Figure-3A). The retroperitoneal mass had spontaneously decreased in size, from 46 to 35mm (largest diameter) during the 4 weeks between the first CT scan and the second biopsy.

To summarize, each patient presented with abdominal pain and leukocytosis revealing gas-containing retroperitoneal mass and hypoechoic hypovascular area with microlithiasis in the testis. In all three cases, tumor markers including lactate dehydrogenase, α-fetoprotein and human chorionic gonadotropin levels were normal.

Pathological examination has been a challenge to diagnose BOTT with metastatic nodes (Figures 3B and 3C).

After orchiectomy, each patient received chemotherapy by Bleomycin, Etoposide and Cisplatin. They are still free of disease after 14 years (Case-1), 8 years (Case-2) and 1 year (Case-3) of follow-up.

**Figure 1 - Abdominal contrast-enhanced CT-scan axial cut showing gas-containing retroperitoneal mass (white arrows).**

![Figure 1](image1.png)

**Figure 2 - Testicular Color Doppler Ultrasound of three patients (in the same order) demonstrating avascular hypoechoic areas (white arrows) with some microlithiasis suggestive of burned out tumors.**

![Figure 2](image2.png)
DISCUSSION

Most reported BOTT are discovered because of symptomatic metastatic nodes, such as presenting with back or flank pain (3-5). Generally, presence of gas in a retroperitoneal mass is usually attributed to retroperitoneal-bowel fistula, abscess or superinfection. BOTT revealed by gas-containing retroperitoneal mass have been shown in only one study to our knowledge (2). This unusual presentation led the authors to perform drainage through endoscopic ultrasound-guided transduodenal puncture. Our cases series reinforces the recommendation of performing scrotal physical exam and scrotal US in case of retroperitoneal masses in men, with aim of avoiding inappropriate management such as extensive surgery or percutaneous drainage. In our series, the presence of gas was attributed to tumor ischemic necrosis. Nevertheless, samples should be sent to culture in order to rule out superimposed infection.

The fibrous replacement and the residual seminomatous part in BOTT may be explained by an intensive immunological response. This mechanism has not been demonstrated in the case of BOTT but an autoimmune response was described in a testicular 'in situ' carcinoma (6). Indeed, Lehmann and Müller reported a case in which immunohistochemical examination of the testicular biopsy demonstrated remarkable intracellular and membranous accumulation of IgG antibodies in the atypical spermatogonia. These specific antibodies were found only in the patient’s serum and not in 500 control sera.

The spontaneous regression of the testicular germ cell tumor results in hypoechoic avascular areas corresponding to hyaline fibrosis, and sometimes in atrophy of the testis (7).

Due to the abundance of necrosis, it is sometimes impossible to identify any tumor cell in the retroperitoneal biopsy sample. In these cases, repeat biopsy may be needed. In the second case, the core biopsy was performed with a 16G needle.

Orchiectomy is generally followed by cisplatin-based combination chemotherapy protocols. This therapy is very effective in the treatment of seminomas and non-seminomatous germ cell tumors.

CONCLUSION

Presence of gas in a retroperitoneal mass is an uncommon presentation of metastatic retroperitoneal lymph nodes of testicular cancer.

It is mandatory to perform a testicular ultrasound in the diagnostic process, despite, sometimes, a normal physical examination. Hypoechoic hypo/avascular areas at US may suggest the diagnosis of BOTT. Retroperitoneal biopsy with a
large needle in the less necrotic part may be the key of the diagnosis.

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CONFLICT OF INTEREST

None declared.

REFERENCES

Whole muscle 18F-choline uptake due to intense physical exercise

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INTRODUCTION

We report an 18F-choline PET/CT scan performed on a 74-year-old patient with history of prostate neoplasm in the clinical context of progressive PSA elevation (10ng/ml) with negative imaging tests. Pelvic images were acquired at 5 min. post-injection of standardized radiotracer dose, while whole-body images were obtained 45 and 120 min. after injection (Figure-1; MIP images). A homogeneous increased uptake of tracer in the whole axial and appendicular muscle structures was highlighted in all series. A SUVmax of 4.8, 5.0 and 4.9 were reached in a reference ROI at left gluteus maximus muscle (Figure-1; axial fused images). Additionally, a fracture of the eleventh left rib arch was also observed (head-arrow). An intense basal physical activity mainly based on long walks, farming tasks and dance classes were referred when the patient was re-interrogated. Taking medication that might interfere with tracer distribution, such as colchicine (1), was also ruled out. It is well known that 18F-choline can be uptake in different tissues including striated muscle (2, 3), although it is a poor referred finding which seems to be related to physical activity, being most likely due to increased local perfusion and probably unavoidable to some extent (3). Knowledge of these variability of physiological uptake, benign findings and pitfalls, is crucial in order to get the most out of the scan.

Figure 1 - MIP and fused PET/CT images acquired at 5 min, 45 min and 120 min after intravenous injection of 18F-Choline. An intense and difuse uptake of radiotracer was observed in all the series of the study. The muscle activity was measured by circular ROI in gluteus maximus muscle (axial fused images) demonstrating stable activity throughout the exploration. Incidentally, a fracture of the eleventh left rib arch was also observed (head-arrow).
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Iatrogenic foreign body in urinary bladder: Holmium laser vs. Ceramic, and the winner is...

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ABSTRACT

Introduction: Urological surgery is estimated to be the third most common cause of iatrogenic-retained foreign bodies (1).

Presentation: A 76-year old man was undergoing a transurethral resection of bladder tumor with a 26-Ch continuous flow resectoscope (Karl Storz, Germany). Before starting resection, a detachment of resectoscope sheath tip was noted. The ceramic tip was free-floating in the bladder lumen, and it would not fit within the sheath, making direct extraction using the loop impossible. An attempt was made to break it with a stone punch, but it was unsuccessful due to impossibility of closing it in the branches. Therefore, we decided to fragment the tip with holmium laser (RevoLix®, LISA Laser products, Germany), using an 800-micron, front-firing fiber. Laser device was settled at with 2.5 J energy and 5 Hz frequency. Ceramic appeared very hard, but it was difficult to carry on breaking with this setting because of tip retropulsion. Then, laser setting was switched to lower energy and higher frequency (1 J and 13 Hz). This setting guaranteed the same power of 13 W, but with minimal retropulsion.

Results: Tip was fragmented against the posterior bladder wall in seven pieces, which were retrieved trough the outer sheath. A total 5.62 kJ were used to fragment it. At the end, superficial lesions of the posterior bladder wall were highlighted. Surgical time was 55 minutes. Patient was discharged home next day without problems.

Conclusions: Holmium laser fragmentation is a safe and effective approach to remove foreign bodies from the bladder.

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Single-Port Trans-Perineal Approach to Cystoprostatectomy with Intracorporeal Ileal Conduit Urinary Diversion and Lymph-Nodes Dissection using a Purpose-Built Robotic System: Surgical Steps in a Preclinical Model

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ABSTRACT

Aim: To report the technique for single-port trans-perineal cystoprostatectomy with intracorporeal ileal conduit urinary diversion and lymph nodes dissection using a purpose-built robotic platform (da Vinci SP1098, Intuitive Surgical, Sunnyvale, CA, USA).

Materials and Methods: In a male cadaver the SP1098 robotic system was used to perform cystoprostatectomy with intracorporeal ileal conduit urinary diversion and lymph nodes dissection by single-port trans-perineal approach. The surgery was completed through a 2.5-cm perineal incision through which a GelPOINT Mini advanced access platform (Applied Medical, Rancho Santa Margarita, CA, USA) and a dedicated 25-mm multichannel port accommodating a 12 x 10-mm oval articulating robotic camera, three 6-mm double-jointed articulating robotic instruments and a 6-mm accessory laparoscopic instrument were positioned. At the planned level of the stoma for the ileal conduit, a 12-mm port was placed through which the EndoGIA® stapler was used to mature the urinary diversion.

Results: The total operative time was 185 min. The procedure was successfully completed without the need for additional ports placement. The benefits of the trans-perineal approach, particularly in longer procedures as radical cystectomy with intracorporeal urinary diversion, might include the avoided need of Trendelenburg position, with undoubtful advantages for the patient and the anesthesiologist in terms of respiratory mechanics and hemodynamics.

Conclusions: The feasibility of single-port trans-perineal cystoprostatectomy with intracorporeal ileal conduit urinary diversion and lymph nodes dissection using the SP1098 purpose-built robotic platform is demonstrated. The duplication of the described surgical steps in the clinical model is awaited when the platform will be available on the market.

CONFLICT OF INTEREST

None declared.
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Sacrospinous hysteropexy with a low weight transvaginal polypropylene mesh for treatment of complete uterovaginal eversion

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ABSTRACT

Introduction: Pelvic Organ Prolapse (POP) is a common condition in elderly resulting from the weakening of the organ suspension elements of multifactorial origin. It compromises significantly the quality of life and can affect more than 50% of multiparous women. Stage IV prolapse or complete uterovaginal eversion corresponds to 10% of the cases and the only form of curative treatment is the surgical correction. The aim of this video is to demonstrate our technique of sacrospinous hysteropexy with a low weight transvaginal polypropylene mesh for treatment of this challenge condition, focusing on technical details in order to prevent mesh related complications. Major, but rare complications, include: infection, prolapse recurrence, abscess formation, bladder perforation and urinary fistula. These situations are related mostly to low volume centers.

Materials and Methods: A 70 years old female with a stage IV POP had obstructive lower urinary tract symptoms. Only after reducing prolapse, it was possible to urinate, but without stress urinary incontinence. No topic estrogen was prescribed before the surgery and she also didn’t take any kind of hormone replacement therapy. Transvaginal ultrasound and the Pap smear screening were done with normal results. Cystoscopy wasn’t employed at anytime of this procedure. Hydrodissection of vaginal wall was followed by longitudinal incision from the level of bladder neck to the cervix. Notice that the ideal dissection should maintain the vaginal thickness, and address the plane of the connective tissue between the bladder and the vagina. Bladder base is then released from the anterior aspect of the cervix in order to create a site to pericervical ring repair and to fix the apex of the Calistar Soft® with polypropylene 3.0 stitches. A blunt dissection extended downwards through the lateral aspect of the levator ani fascia till the identification of the ischial spine and sacrospinous ligaments bilaterally. Two polypropilene 2.0 threads mounted on a specially designed tissue anchor system (TAS) are then fixed into each sacrospinous ligament 1.5 to 2 cm away from the ischial spine and repaired for further prosthesis anchoring. Then, a longitudinal incision is done at the posterior vaginal wall and the recto-vaginal fascia detachment from the posterior aspect of the pericervical ring is identified and corrected with interrupted polypropylene 2.0 stitches to the cervix and to the pericervical aspect of elongated uterosacris ligaments bilaterally. The Calistar Soft A (anterior) and P (posterior)® prosthesis were fixed at the anterior and posterior aspects of the cervix, respectively, with interrupted polypropylene 3.0 stitches and meshes’ arms are fixed to the sacrospinous ligament using the previously implanted TAS. Then, the distal Calistar Soft A® arms were bilaterally fixed into the internal obturator muscles using its fish spine–like multipoint fix device in order to prevent mesh folding. Finally, perineal body repair was done and vaginal wall was closed with individual absorbable interrupted polyglactin 2.0 sutures and a 16 Fr Foley catheter as well as a vaginal pack embedded on neomicin-bacitracin cream were kept overnight.

Results: A high satisfaction rate has been computed with synthetic mesh to POP surgery correction. Approximately 10% of cases of mesh exposure may occur, most of them oligosymptomatic and easy handed by excision or with topic estrogen preparations. After 1 year follow-up, our patient is still satisfied without any complain and no relapse.
Conclusion: We described a successful treatment of stage IV POP in an old female patient. This technique can be used for advanced end stage POP patients, especially those with some contraindication to sacropromontopexy, but who want to keep vaginal length and uterus. Anatomical knowledge, obedience to technical care, and intensive training are the keys for minimizing the risk of complications. Although we had success with this technique, more studies with proper randomization are necessary to compare success and complications of sacrospinous hysteropexy with a low weight transvaginal polypropylene mesh to sacropromontopexy.

CONFLICT OF INTEREST

None declared

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Robot-assisted Simple Prostatectomy with Tunnel-Shaped Trigonization (RASP-TST) – A Novel Technique

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ABSTRACT

To describe a technical modification for robotic-assisted simple prostatectomy (RASP) using three-steps reconstructive technique to achieve a 360° trigonization of the bladder mucosa. Through five-trocars transperitoneal access, we perform a longitudinal incision of the bladder wall and prostate capsule. Our technique of RASP is very similar to the standard operative technique described during laparoscopic and robotic removal of adenoma, however, for reconstruction, we propose the Tunnel-Shaped Trigonization (TST). The first step is the advancement of a bladder mucosa flap until the posterior part of the prostatic urethra. The second step, a running suture between the advanced mucosa and the prostatic capsule is done bilaterally. At this point, the prostate capsule should be totally isolated from the rest of the urinary tract. Finally, the third step is closing both sides of the capsule and bladder mucosa anteriorly identical to a tunnel conformation. Hiding the prostatic capsule optimizes the patient recovery since hematuria is the most related factor for hospital stay length. This pilot-case has shown satisfactory results without the need for continuous bladder irrigation. The prostate volume in the TRUS was 130 cm3 and the preoperative International Prostate Symptom score was 24. He was discharged at second postoperative day and no late complications were detected. In conclusion, the TST-RASP seems to be a safe and feasible modification of the RASP. We hope that the application of the TST can lead us to lower rates of blood loss, transfusion and postoperative complications in comparison to the standard technique.

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CONFLICT OF INTEREST

None declared.

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Robotic partial nephrectomy after pazopanib treatment in a solitary kidney with segmental vein thrombosis

Juan D. Garisto 1, Julien Dagenais 1, Daniel Sagalovich 1, Riccardo Bertolo 1, Brian Rini 1, Jihad Kaouk 1

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ABSTRACT

Objective: To demonstrate our surgical technique of robotic partial nephrectomy (RPN) in a patient with a solitary kidney who received neoadjuvant Pazopanib, highlighting the multidisciplinary approach.

Materials and Methods: In our video, we present the case of 77-year-old male, Caucasian with 6.6cm left renal neoplasm in a solitary kidney. An initial percutaneous biopsy from the mass revealed clear cell RCC ISUP 2. After multidisciplinary tumor board meeting, Pazopanib (800mg once daily) was administered for 8 weeks with repeat imaging at completion of therapy. Post-TKI image study was compared with the pre-TKI CT using the Morphology, Attenuation, Size, and Structure criteria showing a favorable response to the treatment. Thereafter, a RPN was planned. Perioperative surgical outcomes are presented.

Results: Operative time was 224 minutes with a cold ischemia time of 53 minutes. Estimated blood loss was 800ml and the length of hospital stay was 4 days. Pathology demonstrated a specimen of 7.6cm with a tumor size of 6.5cm consistent with clear cell renal carcinoma ISUP 3 with a TNM staging pT1b Nx. Postoperative GFR was maintained at 24 ml / min compared to the preoperative value of 33ml / min.

Conclusions: A multidisciplinary approach is effective for patients in whom nephron preservation is critical, providing an opportunity to select those that may benefit from TKI therapy. Pazopanib may allow for PN in a highly selective subgroup of patients who would otherwise require radical nephrectomy. Prospective data will be necessary before this strategy can be disseminated into clinical practice.

ARTICLE INFO

Available at: http://www.intbrazjuroi.com.br/video-section/20180240_Garisto_et_al
Int Braz J Urol. 2019; 45 (Video #18): 859-859
Re: Antibiotic prophylaxis prior to urodynamic study in patients with traumatic spinal cord injury. Is there an indication?

Michael S. Floyd Jr. ¹, Rauf N. Khadr ¹

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To the editor,

We read with interest the recent paper by da Silva et al. examining effects of antibiotic prophylaxis and risk of urinary tract infection for spinal cord injured patients undergoing urodynamic studies. The authors describe a multi institutional study involving 661 patients who underwent urodynamic evaluation over 2 years (1). Three different antibiotic protocols are described in separate institutions and a cumulative infection rate of 3.18% was found. No differences between patient age or ASIA classification were found to have an association with the development of subsequent urinary tract infection. However, patients with injuries at T6 or above were at increased risk of developing urinary tract infection following urodynamic evaluation (1).

The authors are to be commended for conducting this study as there remains a paucity of literature regarding the topic with only 1 trial to date examining the topic (2).

The authors should acknowledge that the length of time between injury, first and subsequent urodynamic evaluation is not recorded and the rate of autonomic dysreflexia (if any) is not mentioned. It is stated that in the consideration of variables a numbers that several factors were included yet there is no baseline assessment of subjective symptoms based on patient questionnaires such as the neurogenic bladder symptom score (3). In the spinal cord injured patient videourodynamic assessment is the preferred method of urodynamic assessment.

Specific to our Spinal cord injury unit we routinely perform videourodynamic evaluation of spinal cord injured patients both as inpatients and outpatients and all undergo mandatory dipstick assessment prior to the procedure. If suggestive of infection the procedure is deferred but we do not prescribe antimicrobials pre investigation. Additionally we record bladder symptom scores at baseline with a validated questionnaire (SF Qualiveen) and repeat scores following definitive treatment to evaluate response (4).

Yours Sincerely,
Authors

CONFLICT OF INTEREST

None declared.
REFERENCES


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REPLY BY THE AUTHORS: Re: Antibiotic prophylaxis prior to urodynamic study in patients with traumatic spinal cord injury. Is there an indication?

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We thank you for your comments on our latest publication (1). Indeed, what has motivated us the most to carry out this investigation was the lack of evidence concerning the usage of antimicrobials prior to urodynamic studies in spinal cord injured patients (2). An unexpected result for us was the greater incidence of urinary tract infection upon patients with injuries at T6 or above, regardlessly of the use of antimicrobials prior to the procedure.

At this exact moment we are working on a new publication that details the incidence of urinary tract infection specifically amongst the 379 spinal cord injured patients with injuries at T6 or above, now considering the presence of autonomic dysreflexia and urodynamic parameters. The results are becoming clinically relevant.

Yours Sincerely,
Authors

CONFLICT OF INTEREST
None declared.

REFERENCES


To the editor,

Prostate cancer is the second most common cancer in men worldwide. The incidence increases above 50 years. Although prostate cancer is observed in more than 80% of males over 80 years of age, most patients have a slow course and no clinical symptoms. As with all malignancies, early diagnosis is important in prostate cancer. The most important diagnostic methods used in prostate cancer are digital rectal examination, transrectal ultrasonography and PSA. The definitive diagnosis is made by histopathology. Nowadays, it is diagnosed at localized stage (1-4).

The correct staging of the disease after the diagnosis of prostate cancer is very important in terms of the effectiveness and prognosis of treatment planning. In the staging, thoraco-abdominal Computed Tomography (CT), pelvic Magnetic Resonance Imaging (MRI), bone scintigraphy (TVKS), NaF-PET / CT imaging and 68Ga-PSMA-PET/CT imaging, which are currently used as a new diagnostic method, are used. Fluorine-18 (2-fluoro-2-deoxy D-glucose) used in 18F-FDG PET / CT is generally not used in staging because of its low or no involvement in prostate cancer (1-3).

Although the role of 68Ga-PSMA-PET/CT in the management of prostate cancer has not yet taken place in the international guidelines, in the recent studies 68Ga-PSMA-PET/CT staging, treatment plan determination, suspicion of recurrence or biochemical recurrence in the presence of existing lesions has a significant contribution to the evaluation of the response to treatment with high diagnostic accuracy. PSMA is a type II transmembrane protein which increases expression in prostate cancer cells. This can be accurately detected in prostate cancer cells by 68Ga-PSMA-PET/CT examination. However, since 5% of patients with prostate cancer may not have PSMA expression, a false negative result can be obtained with 68Ga-PSMA-PET/CT examination (3-6). In the study performed by Eiber et al., the PSA value of 68Ga-PSMA-PET/CT was 2ng / dl or above, 96.8%, 93% between 1-2, 72% between 0.5-1 and 0,2-0.5. 57.9% of the patients had diagnostic accuracy. 68Ga-PSMA-PET/CT was reported to have high diagnostic accuracy in lesion detection even at low PSA (less than 0.5) (2). Maurer et al. compared the mid-high-risk group with 68Ga-PSMA-PET/CT and conventional radiological imaging (CT or MRI) in nodal smear diagnosed with prostate cancer (130 patients). According to the data obtained, the sensitivity, specificity and diagnostic accuracy of 68Ga-PSMA-PET/CT were 65.9%, 98.9% and 88.5%, respectively, whereas these rates were 43.9%, 85.4% and 72.3%, respectively. The diagnostic accuracy of 68Ga-PSMA-PET/CT was
reported to be higher in nodal staging (3). Pyka et al. reported that $^{68}$Ga-PSMA-PET/CT was more sensitive and specific in demonstrating bone metastasis in a study of $^{68}$ patients with prostate cancer compared with TVKS findings and $^{68}$Ga-PSMA-PET/CT findings (4).

Both primary and definite radiotherapy (RT) can change the target area in salvage RT. Schmidt-Hegemann et al. examined the reliability of the $^{68}$Ga-PSMA-PET / CT, the treatment plan in many patients; both primary definitive RT and salvage can change the target area in RT. Compared with conventional CT, $^{68}$Ga-PSMA-PET/CT reported a significant effect on the radiotherapeutic approach, especially in postoperative patients (5). In a prospective study, Roach et al. evaluated $^{68}$Ga-PSMA-PET/CT images for restaging because of suspicion of recurrence or biochemical recurrence in the middle and high risk group. They found that 51% of the patients’ treatment plan changed when they evaluated the treatment plan with before and after the treatment plan. This rate was found to be 21% for primary staging. As a result, $^{68}$Ga-PSMA-PET/CT reported higher sensitivity in detecting biochemical recurrence (6). In another study, $^{68}$Ga-PSMA-PET / CT and CT were compared in patients with salvage radiotherapy. It has been reported that 28.6% more pathological involvement is detected in $^{68}$Ga-PSMA-PET/CT , CT, and $^{68}$Ga-PSMA-PET/CT has been reported to be more useful in determining RT volume and indication (7). Zamboglou et al. compared $^{68}$Ga-PSMA-PET/CT with MRI for the detection of gross tumor volume (GTV) in primary prostate cancer. It was reported that $^{68}$Ga-PSMA-PET/CT may play an important role in focal radiation planning in lesions (8).

As a result, $^{68}$Ga-PSMA-PET/CT is a more frequently used test because of its high specificity and sensitivity in detecting recurrent lesion and localization even in low PSA levels. In addition, the metabolic activity of the primary site and the local area in the patient with staging as well as the RT plan provides valuable advantages about the width of the RT area. According to all the findings, prospective studies are needed to determine the role and importance of $^{68}$Ga-PSMA-PET/CT in RT plan in prostate cancer.

Yours Sincerely,

Author

CONFLICT OF INTEREST

None declared.

REFERENCES


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