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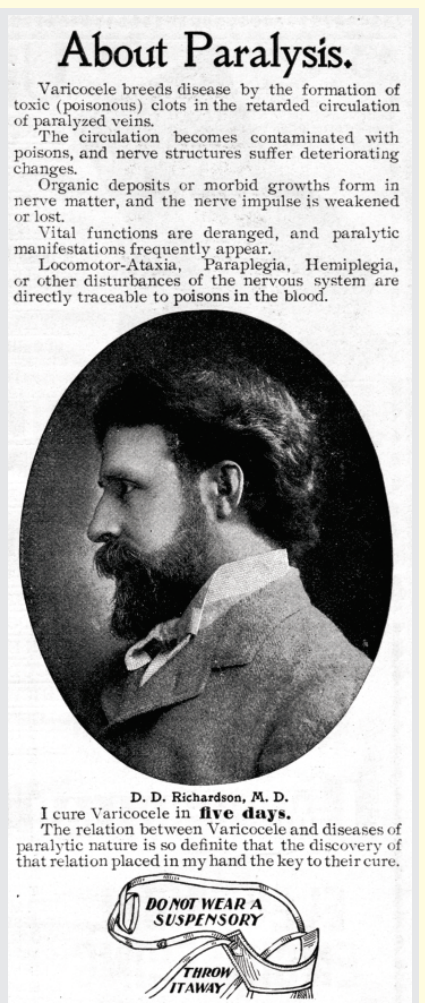

An advertisement in the Chicago Tribune in 1899 heralding the virtues of a varicocele cure in five days. The advertisement states "Do not wear a suspensory. Throw it away". (Page 566)

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EDITORIAL
IN THIS ISSUE

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Urological myriad

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The internationality and diversity of subjects have been remarkable characteristics of International Braz J Urol, an open free access urological journal, as is this issue.

Collaborative multicenter studies in Urology are lacking in Latin American; efforts in this way are welcome by International Braz J Urol. Colleagues from Mexican centers and São Paulo University (Manzo and Vicentini, respectively), found differences in the management of kidney stones with percutaneous nephrolitotomy when compared trained and non-trained urologists. In that survey, they evaluated data from 331 urologists from 15 Latin American countries, that answered a 27-item questionnaire, easily accessed by mobile phones. Patel and Monga, from Cleveland Clinic, present in this issue, the distinct physical and mechanical properties of different ureteral sheaths, that are commercially used in their country, reiterating the possible impact in clinical practice.

Every year, thousands of men worldwide develop recurrence of prostate cancer after the use of external beam or interstitial therapy for primary tumor treatment. Although the vast majority of these patients has been treated with androgen deprivation therapy, local salvage treatments can offer oncological control without the metabolic side effects of hormonal therapy. However, local salvage procedures may result in several urinary and sexual alterations. Recently, the literature is profuse in debates regarding the pros and cons of several options for second local treatment in this population. In the difference of opinion section, we have confronts of arguments favoring salvage radical prostatectomy (Drs. Reis from UNICAMP, Campinas, São Paulo, Brazil and Nguyen from Dana Faber, from Boston, USA), salvage cryotherapy (from Denver University group, with Drs. da Silva and Kim), and about salvage HIFU (A.C. Camargo's' team, from São Paulo).

Active surveillance is a changing paradigm in the last years for stage I testis cancer. Dr. Jain et al. after a national survey that encompassed more than 300 radiation oncologists from United states, observed that a significant percentage of them are not confident in offering surveillance for stage I seminoma patients; there are concerns about the real adherence of patients to the protocols and fears of results of salvage treatments in cases of progression, among other reasons.

Contrary to verified in Eastern world, a Shanghai's group revealed in a large cohort of Eastern Chinese descendants, that the polymorphisms of PCA3 marker were not associated with prostate cancer risks, warranting the need for more investigations about cancer heterogeneity in different ethnicities on Earth.

Moving to uropediatry, Turkish colleagues from Hasekiand Istanbul, demonstrated almost 70% of success with endoscopic use of a non-biodegradable compound in 39 children with vesicoureteral reflux. Uropediatric team from Tehran University, describe the positive results of the use of a plastic wrap barrier as a coverage for the exposed mucosal template in bladder extrophy, before surgical reconstruction.

Reduction of polyps size, skin allergy reactions, without pre-malignant alterations were described with this polyvinylidene chloride (PVdC) barrier.

Three groups from Rio de Janeiro (Hospitals Souza Aguiar, da Lagoa and State University of Rio de Janeiro, UERJ) described the characteristics of penile fracture in a group of men who have sex with men (MSM). They found a specific sexual position associated with these severe fractures and they reported that in all cases diverse sexual dysfunctions (erectile dysfunction, orgasmic and ejaculatory abnormalities, pain during intercourse) or aesthetical dissatisfaction were present after the treatment in all cases of MSM group. Researchers from Italy (Trieste and Bologna) and from London, investigated the differences of patients' perception of their penile angulation in comparison with objective measures performed by experts. There were no conformities in perceptions of the curvatures in patients with Peronye's Disease in men with congenital penile curvature.

Lourenço et al. from Hospital Albert Einstein and Santa Casa de São Paulo, reported similarity in the functional outcomes and quality of life with the use of homemade and commercial transobturatory slings, for female urinary incontinence. This finding is relevant in developing countries, where healthy costs are a permanent question when synthetic materials are used in surgery.

History of Urology in an interesting field of knowledge. Antonio Marte from Bologna, presents a huge historical manuscript focused in varicocele, containing interesting information and illustration from ancient times until nowadays.

In the video section, we have interesting movies from several continents. Among these videos, that of Dr. Almeida e Paula et al., from Presidente Prudente, Brazil, demonstrated a challenging case: a laparoscopic resection of a 10 cm right side functional adrenal pheocromocytoma in a 24-week pregnant woman, with prominent symptoms and inferior vena cava compression.

Enjoy yourself with the myriad of international Urological experiences in this International Braz J Urol edition.

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EDITORIAL

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Network meta-analysis, a new statistical technique at urologists' disposal to improve decision making

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INTRODUCTION

Systematic reviews have been determined to be fundamental tools for establishing the magnitude of an effect, with adequate rigor, methodology and scientific quality (1-4). A meta-analysis is a statistical analysis used in medical investigation, to synthesize information, and compare at least two interventions at a time, regarding an appropriate investigative question (4). Additionally, the available comparisons have to be made, in at least two studies, between intervention A and B otherwise, it is not possible to make it; nonetheless we lack of studies which make all the possible comparisons feasible nowadays (5).

Due to the lack of direct evidence, tools as network meta-analysis and indirect comparisons have been developed, considering all the available studies, and allowing comparisons regarding a common element, to estimate the effect of an intervention in an indirect way (6, 7). Network meta-analysis has also been called multiple-treatment comparison or mixed-treatment comparison meta-analysis (8).

The aim of this review is to expose the introductory concepts of network meta-analyses, and indirect comparisons.

WHAT IS A NETWORK META-ANALYSIS ABOUT?

Meta-analysis allows to statistically synthesizing the available evidence of studies about a clear clinical research question from an adequate systematic review (3, 9). Additionally, network meta-analysis is a tool designed to evaluate the effectiveness when comparing different treatments with similar characteristics, which have not been directly compared in a study. This is a very frequent case, given that there are no enough studies making comparisons for every intervention, because of the cost, complexity and ethical components. Unlike the traditional meta-analysis, which summarizes the evidence from experiments that have evaluated the same comparison (Intervention A vs. B), this new tool compares the results of different studies that have a point or a common intervention (8, 10).

Network meta-analyses, as we have previously said, are also known as multiple-treatment comparison meta-analysis or mixed-treatment comparison meta-analysis; they allow elucidating indirect estimates when comparing different treatments. The statistical methods used by the network meta-analysis, such as the Bayesian and the frequentist methods, have been described in detail in other publications (11, 12).

At this time, let me suppose a systematic review that evidences experiments comparing treatment A vs. B and others that compare treatment A vs. C. With a conventional meta-analysis,

only these kind of interventions could be compared but it would not be possible to make a comparison of A vs. C, which could be clinically important. In these occasions, the meta-analysis of indirect or network comparisons, would be useful.

Whenever it is possible to find estimates of the effect of both direct comparisons and indirect comparisons, the information gathered could increase the precision and power of the effect estimate (8, 13). Indirect comparisons require to establish concepts such as: *transitivity and consistency* that I will explain later (6).

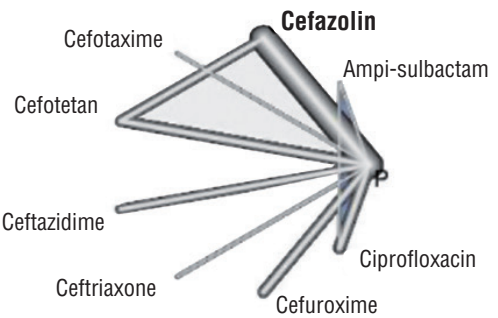
The geometry of the network

The graphic representation of the network will play a fundamental role in the transparency of the results and in the critical reading of it. This allows us to understand in one way or another, the strength of the evidence, the number of articles from which the information presented comes from (treatment nodes), the comparisons that have direct comparisons and those that present indirect or mixed comparisons and the number of patients with different comparisons, in such a way that confidence in the results is increased (8, 13, 14).

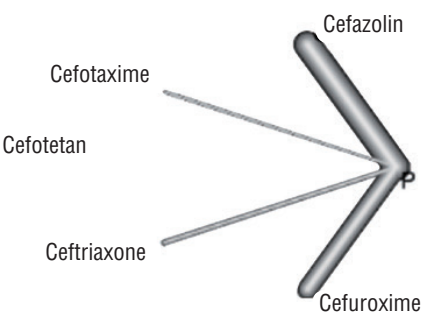
When there is no evidence of union between two pairs of nodes, it means that no clinical experiments were identified for those specific treatments. There are different geometric shapes, depending on the clinical conditions that were studied. For example, if all the experiments are compared with placebo, the geometry will be of a star, on the other hand, if all the interventions are compared with the others, then it will be in the form of a polygon (14) (Figure-1).

Figure 1 - Examples of the geometry of the network.

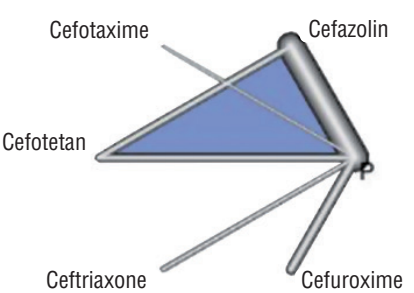
a. Surgical Site infection



b. Intra-abdominal infection



c. Distant infections



Concepts of validity of network meta-analysis: transitivity and consistency

For indirect or mixed comparisons, the studies must be comparable in terms of their design, the population, the duration of the treatment, the final outcome, as well as the variables that could modify the effect, in such a way that there is clinical homogeneity (13). On the other hand, validity depends on a series of concepts and assumptions such as: *transitivity* and *consistency* or *coherence* (16-18). The first one refers to supposing that if intervention B is better than A and intervention A is better than C, then B is better than C. The second one refers to the level of agreement between direct and indirect comparisons.

The t*ransitivity* and *consistency* conditions should be evaluated in all network meta-analysis, however, t*ransitivity* should be specially evaluated in indirect comparisons (6).

There are some conditions to determine transitivity (13):

1. The common comparator must be similarly defined when it appears in

direct comparisons A versus B and B vs. C. Sometimes a certain flexibility can be allowed, although this must be supported by literature.

2. In those studies, that have no arm or intervention C, it is assumed that the absent arms are due to chance. Transitivity will not be met if the choice of the comparator is associated with the relative efficacy of the interventions.
3. Studies with direct comparisons A vs B and B vs C, do not differ with respect to the distribution of possible modifying variables of the effect. In the assumption that there are new and old treatments, in which some variables may change over time, these could be effect modifiers.
4. Patients randomized in direct comparisons could be assigned to any of the treatments (A, B or C).

Consistency, on the other hand, assumes that direct and indirect evidence are estimates of the same parameter. That is, if the additional arm had been included in the experiments A vs B and B vs C, the estimate of the effect should have been similar. There should be no discrepancies among the effect of treatments between direct and indirect comparisons (indirect CA = direct CA) (14-18).

Consistency can be evaluated and verified through statistical tests using different statistical tests such as: Bucher method or inconsistency factors (5, 14, 18).

Network meta-analysis not only shows a numerical result; it can also show a qualitative component that allows to show gaps in research for the generation of new ideas. It might also evaluates the presence of biases, for example, reporting and publication biases, as well as suggesting subgroups analysis (19).

This novel statistical technique could estimate a ranking or classification of treatments according to the probability of being the best or most effective intervention. This is determined by a concept called SUCRA (Surface Under the Cumulative Ranking Curve) (20). This type of organization offers the clinician a better way of interpreting the results, to be applied to patients. However, before focusing on this aspect, a solid structure of the network and an appropriate systematic review should be considered to be able to trust the findings (4, 8).

Writing the Network Meta-analysis

The actual recommendation is based on an actualization of the conventional PRISMA for systematic reviews that involve network meta--analyses, and so it has been named PRISMA--NMA. This checklist-model consists of 32 items, and this tool will allow an adequate report of this new statistical method, given some fundamental points (Table-1) (21-23).

TECHNIQUE LIMITATIONS

As systematic reviews and meta-analysis are not a *panacea*, and should be conducted under strict and specific methodology conditions, indirect/mixed-treatment comparisons and network meta-analysis have also some potential risks. For example, both *transitivity* and *consistency* conditions, must be met, however, very frequently, publications using this novel technique, forget to assess and state them. Additionally, it should be said that the methods are still being developed, and so they are still of low statistic value, but they have a very promising future (9, 16, 17, 24).

On the other side, the related methods could under or overestimate the effects of treatments, compared to the evidence that comes from direct comparisons (25-27). Further advances in different statistical techniques are still required, in order to increase the available knowledge and so enhance its generalization and applicability on decision making (6).

CONCLUSIONS

Systematic reviews and network meta--analysis, constitute a tool that can contribute to clinicians and investigators making decisions regarding patients' treatment.

This new methodology involves conducting an excellent, exhaustive, and rigorous systematic

Table 1 - PRISMA NMA Checklist (23).

Title	
Title	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).
Abstract	
Structured summary	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Others: primary source of funding; systematic review registration number with registry name.
Introduction	
Rationale	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.
Objectives	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
Methods	
Protocol and registration	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.
Eligibility criteria	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).
Information sources	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Geometry of the network	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.
Risk of bias within individual studies	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.
Planned methods of analysis	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: Handling of multi-arm trials; Selection of variance structure; Selection of prior distributions in Bayesian analyses; and Assessment of model fit.
Assessment of Inconsistency	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found
Risk of bias across studies	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: Sensitivity or subgroup analyses; Meta-regression analyses; Alternative formulations of the treatment network; and Use of alternative prior distributions for Bayesian analyses (if applicable).
Results	
Study selection	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Presentation of network structure	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.
Summary of network geometry	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.
Study characteristics	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	Present data on risk of bias of each study and, if available, any outcome level assessment.
Results of individual studies	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.
Synthesis of results	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.
Exploration for inconsistency	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.
Risk of bias across studies	Present results of any assessment of risk of bias across studies for the evidence base being studied.

Results of additional analyses	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).
Discussion	
Summary of evidence	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).
Limitations	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).
Conclusions	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
Funding	
Funding	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.

Abbreviations: PICOS = population, intervention, comparators, outcomes, study design; * Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement. † = Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

review, that will serve as a source of information and ideas. We suggest further training in these techniques for readers, editors, reviewers, and investigators, in order to improve the quality of publications in biomedical journals.

CONFLICT OF INTEREST

None declared.

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DIFFERENCE OF OPINION

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Prostate Cancer – Local Treatment after Radiorecurrence: HIFU – High-Intensity Focused Ultrasound

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Keywords: High-Intensity Focused Ultrasound Ablation; Prostatic Neoplasms; Radiotherapy

Currently, about one third of all newly diagnosed prostate cancer patients select radiotherapy or brachytherapy (BT) as their primary treatment (1). Primary external beam radiation therapy (EBRT) in localized prostate cancer has a risk of biochemical recurrence about 30-60% (1, 2). The most widely utilized criteria for EBRT biochemical relapse is the Phoenix definition (2006). It is established as a PSA elevation of ≥ 2 ng/mL above the nadir PSA (3).There are a variety of treatment options, like watchful waiting, androgen deprivation therapy (ADT) and local salvage therapies. None of them are accepted as gold standard salvage treatments. Another important point is that recurrences are associated with an increased risk of death, metastases and local complications, such as ureteral obstruction, hematuria and pelvic pain (1).

Recent scenario shows that about 70% of these patients receive ADT, but with a decreasing trend over the time (4). ADT is not a curative treatment and it is associated with significant side effects, such as cardiovascular events, sexual dysfunction, humor disabilities, loss of bone mineral density and muscular atrophy. Indeed, proper salvage treatments are mandatory, especially in patients with good health status. We think that, among this population of men underwent upfront ADT, it is possible to select patients which can be submitted to local salvage procedures.

Salvage treatments for local recurrences are adequate after excluded systemic disease with a confirmatory biopsy sample of prostatic tissue and imaging modalities, such as magnetic resonance imaging, computed tomography, bone scan or even combined nuclear medicine techniques (choline PET/CT and PSMA PET/CT). Salvage local treatments are characterized by significant morbidity, with increased risk of rectal injuries and post-treatment incontinence or urethral stenosis that may be as high as 50% (5).

Salvage radical prostatectomy (SRP) is an accepted challenging alternative, due to the fact it is associated with a high morbidity rate, however less than 1% of patients in that situation receive this kind of approach (4). Reports have shown a 5-year and 10-year biochemical recurrence free rates of 47-82% and 28-53%, respectively, and a 5-year and 10-year cancer specific survival of 70-83% and 54-89%, respectively (6). A recent review by Golbari et

al. evaluated the complication rates of SRP. Urinary incontinence varied from 20%-78%. Bladder neck contracture/urethral stenosis occurred in up to 42%. Rectal injury varied from 0-12.5% and erectile dysfunction, in the majority of studies analyzed, occurred in more than 70% and up 100% of the cases (1).

In 2011, Chade et al. reported a retrospective study with 404 radio-recurrent prostate cancer patients submitted to SRP. Pre-salvage PSA and post-RT prostate biopsy Gleason score were the main prognostic factors for biochemical failure and metastases (7).

The eligibility criteria demand an expert team, a long-life expectation, comorbidities and an initial favorable case (mobile prostate in digital rectal exam, no severe rectitis or cystitis). If patients present severe urinary dysfunctions secondary to chronic actinic complications, additional surgical procedures, such as urinary diversion, or bladder augmentation e.g. can be necessary.

The motivation to develop more feasible salvage local therapies has brought us the alternatives of salvage cryoablation and salvage brachytherapy. Reports about salvage cryotherapy have shown acceptable oncologic outcomes with a biochemical recurrence-free survival (BRFS) rate ranging from 28 to 87% (1). Additionally, these reports presented lower complication rates compared to SRP. Lian et al. analyzed the results of salvage cryotherapy with a third-generation technology after radiation therapy. The results were a 5-year BRFS of 43.5%, a urinary incontinence rate of 12% and erectile dysfunction in 57% (8). Another larger study reported urethral stricture in 5.5%, a bladder-outlet obstruction requiring transurethral resection (TURP) in about 4% and the necessity of sling or artificial urinary sphincter (AUS) placement due to urinary incontinence in almost 3%. Related to the performed technique, perineal pain is a possible problematic complication of cryotherapy occurring in up to 8% (9).

High-intensity focused ultrasound (HIFU) is a minimally invasive local ablative technique used either in the primary setting or in the salvage treatment (S-HIFU) of prostate cancer. First reports with this technique occurred in the 1990s. Currently, there are three commercially available devices (Sonablate – Focus Surgery Inc., Ablatherm – EDAP-TMS SA and Focal One – EDAP-TMS SA). It uses a transrectal piezoelectric ceramic transducer focusing on the target that causes thermal, mechanical and cavitation effects, producing a coagulative necrosis in the prostate (9). Temperatures achieved are above 80ºC and there are safety features like a cooling system maintaining rectal mucosa at lower temperatures, a real time 7.5 Mhz. ultrasound visual supervision, continuous measurement of distance between rectal wall and the target, several security alarm levels, and a patient movement sensor (with millimetric sensibility).

S-HIFU is a minimally invasive procedure, requiring regional anesthesia in the vast majority of patients, with virtually no bleeding or associated post operatory thromboembolic events. The majority of the patients are discharged on the first operatory day. In this way, older or patients unfit to undergo a major procedure as SRP, could be candidates for S-HIFU prostatic ablation. Patients refractory to surgery can find in S HIFU an option for their recurrences after radiation therapy.

Factors implicating the prediction of progression are higher pre-EBRT PSA, higher pre-salvage HIFU PSA, PSA nadir > 0.5 ng/mL after S-HIFU and shorter time until PSA nadir (1). Main contraindications for the procedure are inflammatory rectal disease, non-treated urinary tract infection, uncorrected coagulopathy, anal or rectal stenosis, rectal wall thickening > 8 mm (more common in irradiated patients), and prostate volume > 40 mL. Last situation, prostate must be downsized by TURP before the procedure or even previous ADT (10).

After S-HIFU, European literature provides us some studies like Berge et al. that reported 46 patients showing a necessity of TURP for stricture/necrotic tissue in 4.4% and rectourethral fistula in just one case. Urinary incontinence grade II occurred in 15% and grade III, in 2% and erectile dysfunction was registered in 71% (10).

The largest series published to date on salvage HIFU therapy is by Crouzet et al. The group reported a mean 48-month follow-up with 290 patients submitted to whole-gland therapy. Median nadir PSA reported was 0.14 ng/mL and cancer-specific and metastasis--free survivals were 80% and 79%, respectively (11).

Siddiqui et al in Canada published a prospective trial showing a 5-year BDFS of 53% (in a series which only 37% of patients presented Gleason score ≤ 7 (3+4/ prognostic Group 2)), and the rest presented Gleason patterns 4, 5 (prognostic groups 3-5), or unknown) 3% (12). Previously, Murat reported BDFS of 73% in 18 months and Gelet et al. had a negative biopsy rate of 80% in 15 months using Ablatherm system (13, 14).

A recent North American prospective trial by Jones et al. with 100 patients reported that 50% achieved their 1-year endpoint of PSA nadir < 0.5 ng/mL and a negative biopsy (15). Dason et al. in another recent study reported no rectourethral fistulas, no osteitis pubis and just one case of urethral stricture on 24-eligible patients with a median follow--up of 31 months (6).

Last issues discuss the feasibility of the focal salvage HIFU which is based in the fact that about 66% of men who have localized failure after EBRT can develop recurrent unifocal or unilateral cancer, and the main site of recurrence is usually the site of the index lesion before EBRT (16). The recent advances of the prostatic multiparametric magnetic resonance and the image fusion techniques (with ultrasound) can help the planning of focal S--HIFU. In theory, focal treatments can result in less toxicity. Focal treatment can be either a quadrant ablation, a hemi-ablation or the index lesion ablation (with a surround security margin). Ahmed et al. in 2012 registered a BDFS of 49% in 2 years, an incontinence rate of 12.8% and a worsening of the International Index of Erectile Function-5 (IIEF-5) score from 18 ± 16 to 13 ± 21 at 6 months (16).

S-HIFU must be considered an important option in this setting. Selection of appropriate patients will provide a significant oncological control and lower rates of symptomatic complications compared to SRP. Patients with apical tumors should be informed of the risk of urinary incontinence (17). The best lower limit considered is about 6mm from the apex (10). Longer follow-up series and more prospective trials are important to support the current data.

At AC Camargo Cancer Center, between 2011-2018, from a total of 365 patients underwent HIFU, 37 (10.1%) were submitted to S-HIFU, being 35 (94.6%) whole gland S--HIFU and 2 (5.4%) focal S-HIFU; 29 (78%) cases corresponded to failures after EBRT and 8 (21%) after interstitial brachytherapy.

The mean age was 65 years old, the median pre operatory PSA, was 7.0 ng/mL. The median PSA nadir was 0.3 ng/mL. In 3-years of follow-up, 11 patients (29%) had recurrence. Biochemical and clinic failure were verified respectively in 9 (24.3%) and 2 patients (5.4%). There was not blood transfusion, or thromboembolic events. Main complications included urinary tract infections in 5 cases (13.5), urinary obstruction in 7 cases (18.9%) and rectal fistula in 1 case (2.7%).

In one patient procedure the procedure was aborted due to rectal wall thickening > 8 mm, and in other one, due to insurmountable anal stenosis.

In summary, there is an increase amount of patients presenting failure after EBRT or brachytherapy. In the future, with aging of population, this cluster of prostate cancer patients will become greater. Many of them are not adequate candidates to SRP, and many others are refractory to this challenging surgery and its inherent side effects. For these cases, S-HIFU (focal or whole gland ultrasonic ablation) is a safe, effective and minimally invasive procedure that can result in satisfactory biochemical control of the disease, or can postpone ADT and its adverse repercussions in male health.

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Prostate Cancer – Local Treatment after Radiorecurrence: Surgery - Back to the future?

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Keywords: Prostatic Neoplasms; Salvage Therapy; Radiation

As radiotherapy advances, inadequate deliveries decrease and salvage radical prostatectomy, when necessary, tends to be less challenging with improving oncological and functional results. It treats cancer foci in regions such as apex or periurethral tissue, often spared in ablative approaches to minimize side effects; adds the clear goal of an undetectable PSA; and the opportunity for pelvic lymph-node dissection to potentially treat loco regional micrometastasis.

Up to 50% of men may develop recurrence after definitive radiation for prostate cancer, and about one-third of these men will have a biopsy-proven local radiorecurrence, which occurs due to either inadequate delivery of the prescribed radiation dose or inherent biologic resistance of prostate cancer clones to radiation. Standard of care for these patients has been classically observation followed by androgen deprivation (ADT), which adds substantial morbidity and doesn't offer the possibility of cure.

In selected patients, radical prostatectomy, brachytherapy, cryotherapy, and high-intensity focused ultrasound (HiFU) offer reasonable cancer control outcomes without the need for salvage ADT, which is reserved for situations of clear evidence of systemic disease, with the goal of delaying progression and reducing morbidity and mortality (1).

There are currently no uniform definitions of cancer control and toxicity in the post--radiorecurrence setting, no randomized trials comparing any of local salvage therapies to observation or ADT, and no analysis of the impact of pelvic lymph node dissection. At first glance, one might envisage a central role for the potentially less aggressive local approach offered by ablation strategies as opposed to salvage radical prostatectomy (SRP), mainly because if one has not opted for surgery as the first line treatment, the reasons against surgery will exponentially grow in the salvage setting.

However, in pooled head to head data, even based on the more permissive recurrence definitions of ablative therapies, ablative approaches do not necessarily supplant SRP in terms of oncological results and have also not always exhibited the expected dramatic decrease in morbidity when compared to SRP (2, 3).

As radiotherapy advances and improves over time, inadequate deliveries decrease and when necessary, SRP tends to be less challenging, as evidenced by improvement in surgical morbidity and oncologic outcomes in later series, especially in high volume centers where

Clavien grade 3 or higher complications are uncommon and successfully treated in most cases (2). Also, small technical modifications such as anterior repositioning of the bladder neck outside the radiation field might lead to improved functional results.

A benefit of SRP is that it adds the clear goal of an undetectable PSA and the opportunity for pelvic lymph-node dissection (LND) to potentially treat loco regional micrometastasis and delay further progression, although cancer-specific survival data is still needed (4). Also, the particular pattern of tumor recurrence after RT in the periurethral zone (5) is often spared during certain ablative approaches such as HiFU and cryotherapy, excluding cancer foci in regions such as apex or periurethral tissue to minimize side effects.

Low-risk disease patients show higher chances of cancer control, but also carry a higher risk of overtreatment in the radiorecurrent setting. Identifying better markers of metastatic disease is critical to determining which patients are salvage treatment candidates and current rapidly-improving imaging tools impacting the accuracy to distinguish local from locoregional and distant recurrence play a central role.

Initial low-risk disease, long PSADT, low pre salvage PSA, and a lower Gleason score at the time of recurrence indicate a better likelihood of response to local treatment and both improved patient selection and exclusion of metastatic disease are fundamental, independent of therapeutic choice. While recently introduced whole-body MRI, PET with radiolabelled PSMA, bombesin or uPAR and PET/MRI might improve staging accuracy, no standard protocol has been shown to completely rule out the possibility of subclinical metastases (6).

To minimize overtreatment, patients should have: 1 - life expectancy long enough to benefit from intervention; 2 - a disease that is aggressive enough to warrant salvage therapy; 3 - but not so aggressive that there is a high chance that the patient has disseminated disease beyond the capacity of locoregional treatment for curative intent.

Pending high-quality randomized studies, the patient should be involved in an individualized decision-making process where all treatment options pros and cons should be discussed in a multi-disciplinary team and independent of salvage local treatment choice, patient should be highly motivated and aware of significant morbidity and risk of future multimodal treatment.

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Prostate Cancer – Local Treatment after Radiorecurrence: Salvage Cryoablation

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Keywords: Radiation; Prostatic Neoplasms; Radiotherapy

Radiation therapy (RT) is an effective treatment for localized prostate cancer and approximately 45% of patients diagnosed with localized prostate cancer choose radiotherapy as initial treatment (1). Novel RT technology is evolving, allowing more targeted and higher doses of radiation in the prostate such as three-dimensional conventional RT and intensity-modulated conformal RT.

Currently, PSA is the preferred method to monitor patients after prostate cancer RT treatment, but up to 63% of patients may have elevated PSA within 10 years after RT (2). Ray et al. showed biochemical recurrences (PSA criteria) were 33%, local failure 9%, and distant failure (metastasis) 7% in a multi-institutional study of patients with prostate cancer primarily treated with RT that received 60 Gy or higher. Therefore, it is estimated that annually in the U.S., 45,000 patients will have asymptomatic biochemical recurrence following primary RT (1). For patients with intermediate and high-risk prostate cancer, biochemical recurrence is around 50% within 10 years of follow-up (3).

Patients with biochemical (ASTRO or Phoenix criteria) recurrence after RT should be confirmed to have local recurrence before any salvage treatment is considered. Attention should be given to the amount of time since primary treatment because some studies have shown that around 30% of positive biopsies at 12 months post RT had become negative biopsies at 24-30 months (1-4). Patients with rising PSA and biopsy-proven local recurrence after RT have organ-confined disease in only 20% to 39.5% of cases according to salvage RP literature (5, 6). Other challenges may be present in diagnosing local recurrence such as distinguishing findings of radiation changes from high-grade disease, which can lead to false positive results of the prostate biopsy.

Management of patients with local recurrence of prostate cancer after RT is challenging and there is no consensus on the best approach. According to the CaPSURE dataset, palliative treatment with androgen deprivation therapy (ADT) is the treatment more frequently used for biochemical recurrence following RT (2). Apart from systemic therapy, patients with biochemical recurrence after RT currently have the options of salvage radical prostatectomy (RP), salvage cryoablation (CA), salvage brachytherapy, and salvage high-intensity ultrasound (HIFU). The CaPSURE results show a high proportion of patients with locally advanced disease at the time that salvage therapy is considered. The rationale of salvage treatment is the potential to cure the disease instead of management through palliative treatment with androgen deprivation therapy and chemotherapy.

With the challenges of performing radical prostatectomy after RT such as fibrosis, tissue plane obliteration, high rates of urinary incontinence, major complications, rectal injuries, bladder neck contracture, and blood loss, urologists began offering ablative techniques for local recurrence of prostate cancer after RT.

Cryotherapy became an alternative for salvage RP in patients with locally recurrent prostate cancer following RT because of the potential to reduce morbidity (7). Third-generation cryotherapy devices reduce morbidity because they allow a more precise ice ball formation and the flexibility to place additional probes where needed to selectively target sites of recurrence (7-9). Also, the potential of focal ablation of the tumor instead of whole gland ablation is becoming a hot topic among ablative techniques (8, 9).

PATIENT SELECTION FOR SALVAGE CRYOABLATION

Careful patient selection must be performed for patients with localized prostate cancer recurrence after RT and should include some patient and tumor characteristics before initial treatment. Careful patient selection has shown to have a better likelihood of a favorable outcome.

Ideally, patients should have a negative workup (negative bone scan and pelvic imaging) for metastatic disease and life expectancy >10 years.

Patients with pre-radiotherapy PSA <10ng/ml, Gleason score (GS) <8, clinical stage T1c or T2, and are low-risk showed to have a better outcome after salvage cryoablation (5).

Several studies demonstrated that pre-salvage cryoablation PSA >10ng/ml is a predictor of failure of salvage cryoablation and persistent PSA elevation despite initiation of ADT (5, 6, 10).

ONCOLOGIC EFFICIENCY OF SALVAGE CRYOABLATION

Contemporary studies for salvage cryoablation show promising results and reduced morbidity compared to salvage RP. A large study from the COLD registry showed a 5-year biochemical disease-free survival (bDFS) rate of 58.9% using ASTRO criteria and 54.5% using Phoenix criteria (11). Cheetham et al. reported 10 years of follow-up for patients that underwent salvage cryoablation with biochemical recurrence of 52.2% using the Phoenix criteria (12).

Multiple studies consistently reported bDFS ranging from 34% to 74% with follow-up range of 1 to 10 years.

It is important to notice that there is no established definition of failure in the literature and bDFS rates vary based on the definition criteria of failure adopted by the study. Whole gland cryoablation of the prostate involves preservation of the urethra (with urethral warmer) where some of the prostatic tissue can remain, therefore undetectable PSA cannot be achieved. However, low PSA levels are acceptable, especially if they remain stable over time, and do not automatically reflect treatment failure.

Complications of Salvage Cryoablation

The third generation of cryoablation devices significantly reduced the morbidity associated with the procedure compared to earlier generation devices. Cryoablation still has the same stigma associated with older devices, which turns some urologic oncologists away from offering this treatment option to their patients (7-9). Incontinence rates after salvage cryoablation decreased from 73% with older generation cryoablation device to 9.7% (5). Another study compared complications among different generation cryoablation devices, reporting a significant decrease in complications rates with the new technology (5). Another factor to consider is the correct identification of the external sphincter complex. The identification of the external sphincter complex by transrectal ultrasound is well established and cryosurgeons need to carefully identify and place the thermocouples correctly to prevent damage to the sphincter and avoid incontinence (13).

Acute and long-term complication rates following salvage cryoablation seem to be acceptable for the treatment of such a

challenging patient population. Contemporary studies report mild to moderate urinary incontinence ranges from 6-13% and severe urinary incontinence from 2-4% for salvage cryoablation. Surgeons with more experience in cryosurgery can have much lower urinary incontinence rates (8-9%) and total incontinence in less than 1% of patients (5).

Postoperative urinary retention ranges from 2 to 21% of patients. It is very important to assess patient symptoms, urinary flow, and post-void residual before salvage cryoablation in order to proceed with workup for post radiation urethral stricture. The diagnosis of urethral stricture during the workup of recurrent prostate cancer can preclude salvage cryoablation due to risk of postoperative urinary retention and poor urinary function after treatment.

Erectile dysfunction (ED) is a known risk for patients that are eligible for salvage cryoablation; however, most patients considering salvage therapy already present significant ED following radiation therapy. ED following salvage total gland cryoablation ranges from 69% to 86% (5). Patients should be counseled that ED is a very likely complication for those who elect to proceed with salvage treatment. Salvage focal cryoablation is being considered for highly selected patients with local recurrence and promising results are been reported in a small series of patients (5).

One of the most feared complications of salvage cryoablation following radiation therapy recurrence is rectourethral fistula. The previous irradiated tissue, proximity to the rectum, and a more difficult delimitation of the prostate on live intraoperative transrectal ultrasonography are the challenges that surgeons will face when performing salvage procedures. The lack of experience with prostate ultrasonography and low-resolution equipment may account for the incorrect placement of the probes that can result in rectourethral fistulas. The incidence of rectourethral fistulas for salvage cryoablation is low (0-3%) and typically occurs within the first 25 patients treated by the cryosurgeon (5).

PREDICTORS OF FAILURE OF SALVAGE CRYOBLATION

Spiess et al. identified pre-radiotherapy PSA and initial Gleason score as predictors of salvage cryoablation failure (10). Serum PSA (OR: 3.8) and biopsy Gleason score ≥8 at the time of diagnosis (OR: 2.9) were found to be strong predictors of biochemical recurrence.

Nadir PSA ≥0.6 ng/ml after salvage cryoablation was shown to increase the risk of developing biochemical recurrence at 12 months, and patients with Nadir PSA ≤0.6ng/ml presented bDFS at 12, 24, and 36 months in 80%, 73.6%, and 67%, respectively. Levy et al. also showed that tumor burden measured by number of positive cores to prostate volume was also a prognostic factor for biochemical recurrence (14).

Data of pathology reports from salvage radical prostatectomy showed that viable tumor was found to be in the periurethral tissue in 67% of cases, 7% of which were located in direct contact with the urethra. An additional 17.4% of tumors were found within 2 mm of the urethral wall. These are the areas that cryosurgeons avoid ablating by locating the probe of the urethra at least 5 mm from the urethra and using the urethral warmer to prevent thermal urethral injury (15).

FOCAL SALVAGE CRYOABLATION

Whole gland salvage cryoablation has been performed with acceptable outcomes. In an attempt to reduce even more treatment complications, some authors are proposing a technical modification to ensure tissue preservation by performing focal cryoablation of the area containing the tumor.

In order to accurately identify the area within the prostate containing the tumor recurrence, multiple image modalities have been used such as transrectal ultrasonography with target lesion biopsy and magnetic resonance imaging (MRI) with multiparametric approach (T2-weighted, diffusion-weighted, dynamic contrast-enhanced). The combination of image studies with transrectal or transperineal mapping biopsies (16-18).

Patients who are candidates for focal salvage prostate cryoablation need to have negative workup for metastatic disease, cancer recurrence restricted to one lobe of the prostate and small focus of recurrence. Most studies that evaluated feasibility of focal salvage cryoablation considered focal therapy as hemi-ablation of the gland, preserving the contralateral lobe and contralateral neurovascular bundle (16, 17).

The data regarding focal salvage cryoablation is still limited; however, results seem to be promising and comparable to whole gland ablation. bDFS rates range from 69%-100% in 1 year, 50%-72.4% in 3 years, and 46.5%-54.4% in 5 years (16).

CONCLUSIONS

Overall, patients with local recurrence of prostate cancer following RT are associated with unfavorable prognosis. Advanced pathological stage is present at the time of diagnosis of cancer recurrence in two-thirds of patients.

More restricted criteria for biochemical recurrence are needed to improve early detection of patients with local recurrence. PSA monitoring alone may not be enough to detect cancer recurrence early following radiation therapy and the addition of image studies may benefit patients in an attempt to diagnose recurrence while the disease is still organ-confined. The combination of PSA, image studies, mapping biopsies, and possible new tumor markers may increase sensitivity and specificity of recurrence diagnosis in an early stage, allowing for a cure instead of subjecting patients to palliative treatment with ADT.

Currently, the majority of patients with cancer recurrence following RT receive palliative treatment with ADT despite multiple options for salvage treatment. Salvage radical prostatectomy is the most established procedure for salvage treatment; however, this procedure is technically difficult and associated with high morbidity.

Salvage cryoablation following RT recurrence is a promising alternative to salvage RP with lower morbidity to patients and similar mid-term oncological outcomes. Although long-term data is still pending, salvage cryoablation should be offered as a curative method with fewer complications compared to salvage RP to patients with confirmed local recurrence with no signs of metastatic disease.

Focal salvage cryoablation seems to be an alternative option for patients with unifocal cancer recurrence that are considering salvage therapy but want to minimize severe treatment complications as much as possible. Short-term data shows comparable bDFS of focal salvage cryoablation and whole gland salvage cryoablation. Data regarding salvage focal cryoablation is very limited and longer follow-up is required before focal salvage cryoablation can be considered.

Considering the benefits of ablative techniques (reduced treatment morbidity and comparable oncological outcomes compared to salvage RP), randomized clinical trials should be designed to determine treatment strategies for patients with cancer recurrence following radiation therapy.

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REVIEW ARTICLE

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Clinical and pathologic factors predicting reclassification in active surveillance cohorts

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ABSTRACT

The incidence of small, lower risk well-differentiated prostate cancer is increasing and almost half of the patients with this diagnosis are candidates for initial conservative management in an attempt to avoid overtreatment and morbidity associated with surgery or radiation. A proportion of patients labeled as low risk, candidates for Active Surveillance (AS), harbor aggressive disease and would benefit from definitive treatment. The focus of this review is to identify clinicopathologic features that may help identify these less optimal AS candidates.

A systematic Medline/PubMed Review was performed in January 2017 according to PRISMA guidelines; 83 articles were selected for full text review according to their relevance and after applying limits described.

For patients meeting AS criteria including Gleason Score 6, several factors can assist in predicting those patients that are at higher risk for reclassification including higher PSA density, bilateral cancer, African American race, small prostate volume and low testosterone. Nomograms combining these features improve risk stratification.

Clinical and pathologic features provide a significant amount of information for risk stratification (>70%) for patients considering active surveillance. Higher risk patient subgroups can benefit from further evaluation or consideration of treatment. Recommendations will continue to evolve as data from longer term AS cohorts matures.

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INTRODUCTION

Currently, 15-20% of men are diagnosed with prostate cancer (PC) during their lifetime, but the mortality risk is only 3% (1). The incidence of small, low risk, well-differentiated PC is increasing, mainly as a result of PSA screening and increased intensity prostate biopsy schemes (2). Many of these patients would never develop symptomatic disease during their lifespan and therefore do not benefit from definitive treatment due to the indolent behavior of low risk PC (3, 4). It is estimated that 45% of PC patients diagnosed with PSA screening are candidates for conservative treatment and about 2/3 of these men will ultimately avoid definitive treatment (4, 5). The utilization of AS is increasing and in a recent analysis utilizing the CAPSURE database, the use of AS ranged from 6.7% to 14.3% from 1990 through 2009 but increased sharply between 2010 to 2013 when 40.4% of low risk patients had opted for this approach (6).

AS is an accepted option, and one of first line treatments offered for the initial management of low risk PC patients. Low-risk PC has been defined by D'Amico as Gleason score of 6 or less, PSA less than 10 mg/mL, and a tumor that is either

non-palpable or only palpable in less than half of one lobe of the prostate (clinical stage T1c or T2a) (7). These patients have a low possibility of reclassification with only 16-18% of men requiring treatment at 2 years in several large AS cohorts (8-11). The main objective for treatment planning is trying to achieve the correct timing of curative treatment once previously established thresholds that indicate aggressive disease (disease progression) are reached, in order to preserve quality of life and avoid risk of complications associated with other definitive therapies, including surgery and radiation.

It is expected that up to 30-50% of patients with low risk disease would be upgraded to Gleason score (7 or greater) or upstaged at the time of radical prostatectomy (RP) (12-14). This is clinically important, because Gleason score upgrading including pattern 4 results in worse oncologic outcomes such as increased risk of biochemical recurrence, need for adjuvant therapy and increase of cancer-specific mortality (15). A recent longer-term analysis of an AS cohort demonstrated that patients with GS4 have a higher risk of metastasis (16). It is imperative to define patients at low risk of progression after diagnosis and differentiate them from patients with occult aggressive cancer behavior. It is also important to obtain patient progression data from actual AS cohorts, rather than from radical prostatectomy specimens, which will require waiting additional years for current larger cohorts to mature because of the long disease history.

MATERIALS AND METHODS

A systematic MEDLINE/PubMed review was performed in mid 2016 according to the PRISMA guidelines. The main search terms were "active surveillance", "prostate cancer" and "upgrading" as a secondary keyword, 2168 articles were retrieved, 1599 articles remained after applying limits for papers published after 2008. The search result was first screened for relevance by title and limited to English and Spanish literature, abstracts were read and 83 publications of interest were selected for full text review. The search was complemented with own files articles, hand search and articles suggested by important publications until no additional papers were retrieved. The search sensitivity was evaluated by comparing the articles identified against those already known by the authors and those cited in previous seminal reviews. If an article was missed, the title and abstract where carefully reviewed to identify terms that would improve the sensitivity.

OPTIMAL CANDIDATES FOR ACTIVE SURVEILLANCE

The selection of men for AS has been traditionally guided by clinicopathological features that indicate the patient presents with an organ confined, well-differentiated tumor. Life expectancy and comorbidities are important determinants for a watchful waiting (WW) versus AS strategy. Patients with a limited life expectancy are better candidates for WW which consists of less frequent PSA monitoring, no further prostate biopsies, and the application of androgen deprivation therapy if the disease becomes metastatic. For patients on AS, this switch to WW does not occur infrequently. Stratified by age, 10% of 55-year-old men switched to WW, but 50% of 70-year-old men moved to watchful waiting in one study (17). In WW, a strategy of non-invasive monitoring with PSA and DRE every 6 months leads to very low prostate cancer-specific mortality at 10 years, making this an effective strategy in carefully selected patients (18).

Current available information is limited to non-randomized clinical trials with follow-up of less than 10 years (the majority <5 years) and the recommendation from major clinical guidelines is that AS should be offered only in selected lower risk patients. However, there is no consensus on the optimal method of selecting men for AS, and depending on the clinical guidelines or on studies from different cohorts, selection criteria can change. The National Comprehensive Cancer Network (NCCN) guidelines define very low risk PC as those with T1c disease, Gleason score ≤6, PSA <10ng/mL, fewer than three positive biopsy cores, with ≤50 percent cancer in each core, and a prostate-specific antigen density (PSAD) <0.15ng/mL/g. In this very low-risk group, the NCCN recommends active surveillance as the pre-

ferred option for those with a life expectancy less than 20 years. Very low risk patients in the Epstein criteria employ one or two positive cores, no core with more than 50% involvement and a PSA density of less than 0.15. Epstein low risk disease is defined as Gleason T1- T2a disease along with Gleason score ≤6 and PSA <10ng/mL. In this category, NCCN recommends AS, surgery or radiation if life expectancy >10years (19). The American Urological Association (AUA) (20), and The European Association of Urology (EAU) (21) recommendations are listed in Table-1 with other commonly used criteria.

One concern is limiting this population so severely that relatively few patients would be candidates. Cancer Care Ontario (CCO) guidelines, in addition, recommends GS 7 cancer [3+4], who have low-volume and percentage Gleason 4 pattern pathology (<10 to 20 percent pattern 4), and/or age older than 75 years (22). (Table-1).

Overholser et al. compared outcomes between men with very low risk (Epstein criteria) and low-intermediate risk disease (4 or fewer cores with GS 6 cancer and/or only 1 core of Gleason 3+4 cancer <15%) and found no differences in adverse pathological features such as upgrading or upstaging at radical prostatectomy (23). There was an obvious increase in patients eligible for AS from 44% to 68% of their population by expanding these selection criteria. The risks of adverse specific outcomes will likely be higher with the inclusion of men with more intermediate risk features, but the absolute risk of death may still be low (24). In the previously described study (23), only two of the 320 patients either experienced metastatic disease or died of PC during the 12-year study period. Notably, in the recent TGCA analysis, GS 6 tumors were all diploid, but increased grade greater than 4 was associated with increased polyploidy (25). The new International Society of Uropathology (ISUP) Gleason grade groups classifies Gleason 6, 3+4, 4+3, 8 and 9-10 as grade groups of 1, 2, 3, 4 and 5 respectively (26). The adaptation of this grade system by urologists will witness incorporation of this system in active surveillance protocols.

Expanding criteria for AS without compromising absolute outcomes will be provided in the future with additional follow up in surveillance cohorts.

Mortality and quality of life are indicators that have been infrequently applied to these patient populations and will be an area of development in the future. Bellardita et al. summarized the evidence on quality of life in AS cohorts in a systematic review in 2014 examining ten research based studies that measured this outcome (27). Patients undergoing AS reported good quality of life in diverse questionnaires and did not appear to suffer major psychological

Table 1 - Commonly utilized clinicopathologic criteria for active surveillance.

AS criteria	PSA	Clinical stage	Gleason	Core	PSAD	Age/Life expectancy
NCCN very low risk	10	T1c	6	<3 core / <50%	< 0.15	<20 years
NCCN low risk	10	T1- T2a	6			>10 years
CCO			6	Low volume		
			7 (3+4)	<10 - 20% of 4 pattern		>75 years
AUA	10	T1c - T2a	6			
EAU	10	T1c - T2a	6	< 3 core / < 50%	< 0.15	>10 years

NCCN = National Comprehensive Cancer Network; **CCO =** Cancer Care Ontario; **AUA =** American Urological Association; **EAU =** European Association of Urology; **PSAD =** PSA density

impact, indeed overall scores were comparable or better than those of patients undergoing radical treatment.

Another factor associated with AS is the risk associated with monitoring itself, namely infection or other complications after prostate biopsy (28). A large population based study demonstrated that patients undergoing a transrectal biopsy had more than twice the risk of hospitalization within 30 days of the procedure compared to a control population (29). There is a recent chronological trend towards increased infection with antibiotic resistant organisms after transrectal biopsy (30, 31). Bleeding and pain from the procedure also impact patients undergoing prostate biopsy. Hematuria and hematospermia are common after the procedure, but typically mild and self-limiting (32).

Selection criteria and patient populations continue to evolve because AS cohorts still have relatively short follow-up compared to PC's natural evolution.

CLINICAL AND PATHOLOGIC FACTORS THAT PREDICT RECLASSIFICATION

There is a concern in clinical practice that some patients diagnosed initially as low--risk PC actually have aggressive disease. Many studies have demonstrated the frequent disparity between Gleason scores reported on prostate biopsy and at radical prostatectomy, that is in part explained because of misdiagnosis on first biopsy or also because most AS programs only use Gleason score, clinical stage and PSA to enroll patients. excluding other possible important predictors such as age, PSA density (PSAD), prostate volume, obesity, and race. These features are summarized in Table-2.

Radical prostatectomy specimens provide an opportunity to determine the actual grade and stage of low risk patients in modern cohorts and determine those features that best predict upgrading. Further pretreatment risk stratification in patients labeled as "low risk" is of paramount importance. There are externally validated clinical predictors (nomograms) that could help identifying this population (33). Delaying definitive treatment in this kind of patients could result in disease progression and adverse outcomes (34, 35).

Tumor Volume

In most malignancies, tumor volume is an important indicator for disease aggressiveness as well as in PC, but one unique aspect of PC is its multifocal origin (36). The physician usually has only an indirect estimation of tumor volume in the TRUS biopsy based on the number of cancerous cores, and the percentage of cancer involvement within each core. Unfortunately, at TRUS biopsy, the current standard for PC diagnosis, larger prostates may be under sampled or the tumor volume underrepresented.

Even with the above caveats that TRUS biopsy has, indirect representation of tumor volume by assessing maximal core involvement and number of cores with cancer has been found to be important predictors for GSU, AS failure and functions as a trigger that indicates the necessity of treatment of these patients. Bul et al. found increasing number of positive cores as one of the strongest predictors for reclassification (OR 2.2; 95%CI 1.67-2.81; p<0.001) (8). Klotz et al. described number of cores involved with cancer as a factor that correlates with risk of reclassification in the largest AS cohort described to date (10). Results are corroborated by other investigations (37, 38).

Higher tumor volume has a direct proportional relationship with probability of reclassification on follow-up biopsies and subsequent AS failure. Furthermore, having bilateral tumor in the initial biopsy or developing a bilateral tumor on follow-up biopsies are associated with an increased risk of failing AS because of increasing cancer cores >2, increasing maximal core involvement >50% and Gleason score upgrading (HR 3.8; 95% CI 2.046-7.058; p<0.0001). This association was encountered in our AS cohort [unpublished data].

PSA density

Major AS cohorts and studies have repeatedly demonstrated PSA density (PSAD) can predict progression of the disease. The multi-

Table 2 - Clinicopathologic predictors of upgrading gleason score (>6) during active surveillance from published studies.

Markers	Studies	Correlates	Strength
No. positive cores	Bul et al., Klotz et al., Truong et al., Iremashvili et al.	Higher cancer volume	+++
Max. % core involvement	Klotz et al., Truong et al.	Higher cancer volume	+++
PSA Density	Bul et al., Kobt et al., San Francisco et al., Truong et al., Iremashvili et al., REDEEM	Higher cancer volume, Low testosterone	+++
Small prostate volume	Freedland et al., Davies et al., Gershman et al.	Low testosterone	++
Obesity	De Cobelli et al., Truong et al.	Low testosterone, hyperestrogenism, hyperinsulinemia, elevated adipokines	++
Inherited cancer syndromes	Castro et al., Bratt et al.	Aggressive cancer, metastases risk	+
Hypogonadism	Pichon et al., Gao et al.	Aggressive cancer	+
African American ethnicity	Rebbeck et al., Sundi et al., Abern et al.	Aggressive cancer, advanced stage and poorer outcomes	+
PSA velocity	Kates et al.	Aggressive cancer/ >4 years on surveillance	+/-
Family history	Hemminki et al., Kupelian et al., Kundu et al., Selkirk et al..	Aggressive cancer	+/-

+++ = Strong association; **++ =** Moderate association; **+ =** Weak association; **+/- =** Doubtful association

national European study PRIAS found PSAD to be one of the two strongest predictors for reclassification and switching to definitive treatment (8). Kobt et al. recognized in their AS cohort that PSAD< 0.15 may suggest indolent disease (39) and San Francisco et al. went further and reported that a PSAD greater than 0.08 can predict pathological progression (40). These results were confirmed recently in a larger AS cohort (41). PSA density seems to be a key factor in predicting PC progression, in the first sub analysis of the REDEEM study the authors could not prove dutasteride prevents progression in AS, but found PSAD to be a predictor for disease progression (42). It appears that PSAD should be included not only as a selection criterion but also as a trigger for intervention or as an indicator of AS failure (OR 3.0 (2.14 – 4.28, p<0.01) (8). Smaller prostates are more prone to GSU at radical prostatectomy possibly because a small gland size may be a marker of lower androgenicity, and cancer growing in this environment may have a more aggressive biology as suggested previously (43). Several studies have suggested that lower volume prostates harbor a greater potential for cancer upgrading. Davies et al. and Gershman et al. found a smaller prostate size to be an independent predictor of upgrading OR 0.58 and OR 0.59 respectively, and these results have been corroborated in different publications (44, 45).

Most major urological societies recommend PSAD as a selection criterion in clinical guidelines and AS cohorts (being adopted now in the NCCN guidelines, PRIAS study (8), Johns Hopkins cohort (11) because previous studies not

using PSAD as a cutpoint have demonstrated higher rates of upgrading in AS populations (10, 33).

Obesity

Increased body mass index as a component of the metabolic syndrome is a major risk factor for deleterious chronic diseases like diabetes, cardiovascular disease, hypertension and stroke. Obesity generates high levels of insulin and IGF-1, elevated estrogen, reduced testosterone and increased levels of adipokines that create an environment of chronic subclinical inflammation that would favor the development of more aggressive PC (46). Compared with normal or overweight men eligible for AS, obese patients are at higher risk of upgrading or upstaging. Furthermore, obesity (BMI>32) has been found to be an independent predictor of upgrading of low risk patient biopsies (odds ratio of 1.90) as one of the four criteria assessed in the validated BADGR nomogram (37).

Other Clinical predictors

Other less powerful clinical predictors for reclassification include low serum testosterone and race. Pichon et al. in a cohort taken to radical prostatectomy found GSU from predominant Gleason score 3 to predominant Gleason 4 more commonly in hypogonadal patients (total testosterone <3) when compared to patients with normal testosterone (20.1% vs 11.6% P=0.002) (47). In a more recent trial measured serum testosterone in 167 low risk PC patients eligible for AS that underwent RP revealed preoperative testosterone was lower in the upgraded compared to the non-upgraded group (3.72 vs 4.56, P<0.01) (48).

African American (AA) men have a higher incidence of PC compared to other racial groups, and present with more advanced stages at diagnosis, more aggressive tumors and poorer outcomes (49). It is still uncertain if race is a prognostic factor for upgrading in AS cohorts. African American men with very low risk PC who met the criteria for AS but undergo RP experience significantly higher rates of upgrading and adverse pathology compared to other races (27.3 vs 14.4 P<0.001) (50) suggesting concern for AS in this cohort. However, major AS cohorts underrepresent minorities, only 6% to 10% of those men are African American, thus the oncologic outcomes of this particular subgroup of patients is unknown. In an effort to examine results from AS cohorts, Iremashvili et al. (38) analyzed a cohort of 24 AA in AS and found an adjusted hazard ratio of 3.8 for reclassification on serial biopsy. In a large multiethnic cohort with 39 African American men on AS (Duke Prostate Centre), black race remained the sole predictor of treatment (HR 3.08, P = 0.01) (51). Sundi et al. (52) also reported a significant higher rate of upgrading of AA compared to Caucasian men (32.7% vs 12.6% p<0.001). Further study with larger populations, and subtyping of different AA ethnicities is required before a definitive conclusion can be reached regarding this issue.

Having a first-degree family member with PC increases the risk of PC diagnosis (53). Family history is a well-known risk factor for PC, but literature is scarce and contradictory on whether it is a factor that predicts reclassification and AS failure. Some authors suggest that men with family history of PC have more aggressive tumors compared to patients with sporadic neoplasias (54), but more recent studies have found no difference in tumor features and reclassification among patients with or without PC background in their families (55, 56).

Cancer susceptibility genes (BRCA1-BRCA2) represent a special subgroup in whom there is a clear trend toward more aggressive tumors. These mutations are suspected in patients with strong family history of early breast, prostate and ovarian cancer. Carriers of this mutation are at higher risk to develop more aggressive disease and higher risk of developing metastatic disease. Recent work suggests that this subgroup of patients should not be considered for AS (57, 58).

Iremashvili et al. (59) analyzed the usefulness of PSA kinetics for surveillance of patients on AS. They followed up 314 patients on AS and analyzed PSA and its derivatives namely PSA density, PSA velocity, PSA doubling time and correlated them with the risk of progression on surveillance biopsies, first through fourth. They found that PSA velocity and PSA density were associated with the risk of progression only during the fourth biopsy and hence need a minimum follow-up of 4 years to be an efficient prediction

tool. Kates et al. (60) have observed that using the PC Research International Active Surveillance (PRIAS) protocol, which uses PSA kinetics along with scheduled biopsies at 1, 4 and 7 years compared to the John Hopkins Hospital (JHH) protocol of doing an annual biopsy alone in their AS cohort of 1125 men would increase the chance of an intervention by 12%, thus questioning the validity of PSA kinetics in this setting. Therefore, PSA velocity appears less useful in the short term for predicting risk of failure.

NOMOGRAMS

Multiple prognostic models have been developed to calculate the probability of pathologic features in the prostatectomy specimen such as low grade, low volume or organ-confined disease (35, 37, 61-63), but many nomograms have demonstrated low predictive accuracy and poor calibration upon external validation (Table-3). The utility of the nomograms to predict insignificant disease has been assessed in several studies. Iremashvili et al. evaluated and compared the ability of 4 nomograms (Capitanio et al., Chun et al., Kulkarni et al. and Moussa et al.) to predict GSU and found that all the nomograms were poorly calibrated and not ready for clinical application (63). Wong et al. revisited other four prognostic models and reported only a moderate range of predictive ability for the Kattan et al. model (64).

More recently, the performance of different radical prostatectomy-based prognostic tools in predicting biopsy progression were analyzed (Partin et al., Dinh et al., Kattan et al., Truong et al. and Kulkarni et al.) in AS patients and results indicate that the Kattan and Truong (BADGR) nomograms had a higher predictive value than the other tools and were able also to stratify patients into subgroups with different risk of progression at the time of diagnosis (65). These two nomograms have important differences, which

Table 3 - nomograms that predict pathologic (Gleason >6) upgrading at the time of radical prostatectomy and validation in as cohort.

Nomogram (author)	Patients (no)	Primary outcome	Variables used for formulation of nomogram	Predictive accuracy rrp (auc)	Accuracy in as* (c-index)
BADGR (Truong)	413	Probability of Gleason upgrading	PSAD, BMI, # Positive cores, Max % cancer core involvement	0.753	0.671
Kulkarni	175	Probability of Gleason upgrading	PSA, Age, Pathologist , DRE, PIN, TRUS volume, Hypoechoic lesions on TRUS, Type of biopsy, % Cancer in biopsy	0.71	0.609
Dinh	5,581	Probability of Gleason upgrading	Age, PSA, % positive cores	NA	0.560
Kattan	409	Probability of indolent tumors	PSA, Clinical Stage, Primary Gleason, Secondary Gleason, TRUS volume, Length of cancer & benign tissue in the biopsy material	0.79	0.687
Partin	5,629	Probability of pathologically non organ confined disease	PSA, Clinical stage, Gleason score	0.702	0.537

PSA = Prostate specific antigen; PC = Prostate Cancer; **TRUS =** transrectal ultrasound; **PSAD =** Prostate specific antigen density; **BMI =** Body mass index; **DRE =** Digital rectal examination; **PIN =** Prostate intraepithelial neoplasia

***** Harrel's C- Index based on "Predictive models and risk of biopsy progression in active surveillance patients" by Iremashvili et al. (63)

suggest that a more effective predicting model combining the strong sides of both tools could be developed (Table-3).

Truong et al. assessed more than 30 clinicopathological parameters and using multivariable logistic regression found PSAD, obesity, number of positive cores and maximum core involvement (BADGR nomogram) to be useful for predicting upgrading (Gleason ≥7) on final pathology. An online risk calculator has been provided <https://www.urology.wisc.edu/research/researcherslabs/jarrard/prostate_cancer_predictor> (66). The BADGR and Kattan nomograms are very similar, the main difference between them is the inclusion of BMI and PSAD in the former. Notably, the BADGR nomogram is designed to predict pathological upgrading only for men diagnosed with Gleason 6 PC. The main outcome Kattan´s tool is to determine the probability of pathologically indolent cancer in somewhat higher risk PC, thus the optimization of these two nomograms have a different focus.

EVOLVING TECHNOLOGY FOR AS PATIENTS

The focus of this review was on clinical and pathological parameters for predicting progression of grade on AS. However, newer approaches may help in stratifying patients that have factors that place them outside the very low risk group including MRI and genomic testing. Multiparametric MRI (MPMRI) has been shown to reduce misclassification rates due to biopsy and has been included in the current clinical guidelines in the United Kingdom (67). Although MRI lacks sensitivity for detecting low Gleason score cancer (3+3), this might be deemed an advantage for choosing imaging negative patients for AS (68-70). However, MRI generates significant cost as well as missing roughly one-third of significant PCs (71). Incorporation of MPMRI into contemporary AS protocols will need large prospective trials to assess its impact on AS and the frequency of subsequent biopsies (72). MRI fusion is another technology that needs wider validation, but some studies have suggested it may enhance the detection of clinically relevant prostate cancers (73, 74).

Genome-based tests for detecting higher risk cancers have been a novel addition to the existing armamentarium of tools for stratifying AS patients. More widely validated tests include the Oncotype DX and Prolaris tests that utilize biopsy tissue. Oncotype DX is a 17-gene assay performed on biopsy tissue that has been shown to increase the percentage of patients choosing AS (75). Prolaris bases outcomes on the gene expression profile of 31 cell cycle progression (CCP) and 15 housekeeping genes in tissues obtained at the time of biopsy to predict aggressiveness of PC (76). Newer tests include Promark, a quantitative multiplex proteomics assay based on the expression pattern of eight protein markers to predict aggressive cancer (77). The downside of genomic testing is its significant cost ($3800 USD) potentially limiting widespread usage. In addition, estimates have suggested that the majority of risk, roughly 70%, can be determined by existing clinicopathologic parameters (78).

Finally, newer non-invasive testing may serve as an adjunct for monitoring patients on AS, including the PCA3 test. This urine-based test was analyzed in a longitudinal AS population of 240 men, but did not change longitudinally with grade reclassification (79). In another study, an incremental benefit was seen with PCA3 in an AS population for predicting Gleason >6 (80).

CONCLUSIONS

In order to determine the probability of a patient for disease progression during conservative treatment, it is not enough to extrapolate the information from radical prostatectomy cohorts, but will be imperative to get the data from actual AS patients that progress during follow up. In order to have more accurate data, we would have to wait for the current larger cohorts to mature more, because of prostate cancer´s long natural history.

Currently, the data widely supports the use of very low risk PC features for selection of patients for AS (Gleason T1c, PSA ≤10, Gleason ≤6, ≤2 positive biopsy cores, ≤50% cancer in any core, PSAD <0.15). Nomograms can be further used to stratify patients into higher risk groups for Gleason Score upgrading and subsequent reclassification during AS. Additional factors such as increased cancer volume, higher PSAD, increased body mass index,

African American race or a genetic predisposition play a role in defining this increased risk. Higher risk subgroups may need a closer surveillance with more frequent biopsies (yearly), the inclusion of saturation biopsy approaches, compared to very low risk patients in which less strict protocols may be applied. The wider use of AS will ultimately benefit patients and criteria will continue to evolve as further information from longer-term AS cohorts matures and technology advances.

ABBREVIATIONS

PC=Prostate Cancer
AS=Active Surveillance
GSU=Gleason Score Upgrade
RP=Radical Prostatectomy
PSA=Prostate Specific Antigen
PSAD=Prostate Specific Antigen Density
AA=African American

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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On thin ice: barriers to adoption of surveillance for patients with stage I testicular seminoma. Survey of US radiation oncologists

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ABSTRACT

Purpose: Most men with stage I testicular seminoma are cured with surgery alone, which is a preferred strategy per national guidelines. The current pattern of practice among US radiation oncologists (ROs) is unknown.

Materials and Methods: We surveyed practicing US ROs via an online questionnaire. Respondent's characteristics, self-rated knowledge, perceived patient compliance rates with observation were analyzed for association with treatment recommendations.

Results: We received 353 responses from ROs, of whom 23% considered themselves experts. A vast majority (84%) recommend observation as a default strategy, however this rate drops to 3% if the patient is believed to be noncompliant. 33% of respondents believe that survival is jeopardized in case of disease recurrence, and among these respondents only 5% support observation. 22% of respondents over-estimate the likelihood of noncompliance with observation to be in the 50-80% range. Responders with a higher perceived noncompliance rate are more likely to recommend adjuvant therapy (Fisher's exact $p<0.01$). Only 7% of respondents recommend observation for stage IS seminoma and 45% administer adjuvant RT in patients with elevated pre-orchiectomy alpha-fetal protein levels.

Conclusions: Many US ROs over-estimate the likelihood that stage I testicular seminoma patients will be noncompliant with surveillance and incorrectly believe that overall survival is jeopardized if disease recurs on surveillance. Observation is quickly dismissed for patients who are not deemed to be compliant with observation, and is generally not accepted for patients with stage IS disease. There is clearly an opportunity for improved physician education on evidence-based management of stage I testicular seminoma.

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INTRODUCTION

Testicular seminoma is the most common malignancy among young men, and it is highly sensitive to chemotherapy and radiation therapy with excellent cure rates, even in patients with metastatic disease (1). Virtually all patients with stage I testicular seminoma are cured regardless of post-orchiectomy management, and several large prospective population-based studies revealed no difference in overall survival outcomes in patients treated with adjuvant therapies

or observed clinically (2, 3). Current US national guidelines recommend observation as preferred option for patients with this diagnosis (4). The most recently published National Cancer Data Base analysis revealed a dramatic increase in uptake of observation between 1998 and 2011 (5), yet the survey of practicing radiation oncologists in the United States conducted in 2010 showed an overwhelming recommendation for adjuvant RT and a very poor acceptance of observation (6). We hypothesized that over the past 6 years US radiation oncologists would have embraced observation as the first choice option for these patients, and we wanted to determine if physicians take into consideration clinical tumor features as well as concerns for poor compliance with observation protocol in making clinical recommendations. Finally, the optimal management is unclear for the small percentage of patients with stage I disease who have elevated serum markers after orchiectomy (stage IS). Using an anonymous electronic survey of practicing US radiation oncologists we have set out to examine the most contemporary patterns of practice.

MATERIALS AND METHODS

Survey Instrument Development

The study was approved by the Oregon Health and Science Institute (OHSU) institutional review board. The online survey was developed using the Research Electronic Data Capture (REDCap) software licensed by the Oregon Clinical and Translational Research Institute (OCTRI) for use by OHSU. The survey contained 25 questions regarding respondent demographics and treatment recommendations for various clinical scenarios. Branching logic was used to tailor the questions based on previous responses, such that most respondents were not exposed to all 25 questions. Respondent characteristics included information regarding practice setting (academic or private), years since completion of residency, and geographical location. Additionally, respondents self-rated their depth of knowledge in the field of testicular seminoma and were grouped into three categories - not comfortable with evaluating a patient with seminoma, comfortable with evaluating and treating, and expert level knowledge of the field.

Data Collection

The data sample was collected through a fully anonymous online survey of radiation oncologists in the United States, who are members of the American Society for Radiation Oncology. Each participant was contacted and invited to complete the survey using the REDCap tool. The invitation contained instructions for participation, information regarding the study, and contact information. The first invitation was sent on September 8th, 2016. Participants who requested not to be contacted in the future were immediately removed from the database. The remaining respondents were contacted with a reminder email on September 18th, 2016, to maximize response rate. No further communication with participants ensued.

Statistical analysis

Respondents were characterized by years since residency completion, number of testicular seminoma patients evaluated in the past year, number of testicular seminoma patients treated with radiotherapy in the past year, practice setting, geographic region of practice, and self-rated knowledge. These six factors were analyzed for correlation with respondent treatment recommendations. Pearson's chi-square test was used to examine the correlation between characteristics and treatment questions. Cochran-Armitage analysis was used to assess trends in change of ordinal categorical values. Fisher's exact test was utilized to quantify deviation from the null hypothesis in relatively small sample sizes. A p-value <0.05 was considered statistically significant. SAS 9.4 (NY, Cary) was used for statistical analysis.

RESULTS

Survey Respondents

The survey was sent to 6967 email addresses, some of which could belong to the same individuals as the developed database used both personal and institutional email addresses. We re-

ceived 712 undeliverable/failed automatic responses, 74 non-applicable/ineligible responses, and 354 completed responses, among which one was from a non-radiation oncologist, thus excluded from analysis. Characteristics of 353 radiation oncologists are summarized in Table-1. Most respondents (>70%) were practicing for over 10 years after completing residency training, most (73%) felt comfortable evaluating and treating patients with testicular seminoma and 23% considered themselves experts in this field. Over 30% of respondents did not see any patients with testicular seminoma over the past year and over 50% did not treat testicular seminoma with radiation therapy over the course of the year. Very few (<3%) treated more than 5 patients with testicular seminoma over the past 12 months.

Most Respondents Recommend Observation for Compliant Patients with Stage I Testicular Seminoma

When given a clinical scenario of a 20-year-old man with stage I left-sided testicular seminoma, 84% of respondents recommended observation following orchiectomy, while RT was recommended by 10% and chemotherapy by 6% (Table-2). There was a significant difference between responses from physicians in academic institutions and private practices, with RT recommendation by 3% and 13%, chemotherapy by 9% and 6% and observation by 88% and 81% of academic and private physicians, respectively (p=0.003). Respondents who recommended chemotherapy were more likely not to have seen a single testicular seminoma patient in consultation over the past 12 months, compared to respondents who recommended observation or RT (p=0.02). Respondents who did not treat a single testicular seminoma patient with RT over the past 12 months were more likely to recommend observation or chemotherapy to their patients than RT (p<0.01).

Fear of Perceived Noncompliance with Clinical Follow-up Affects Adjuvant Treatment Recommendation

Among respondents, 22% estimate the rate of noncompliance with surveillance to be 50-80% (Figure-1). The fear of poor compliance dramatically affected the adjuvant treatment recommendations among our respondents, with only 3% still recommending observation, 67% recommending RT, and 30% recommending chemotherapy among those 296 respondents who initially endorsed observation (Table-2). There was a strong correlation between recommending observation in the adjuvant setting and perceiving noncompliance among men with testicular seminoma to be in the low range of 10 to 30%, whereas practitioners who believe the rate of noncompliance is over 30% in general are less likely to recommend observation (p<0.01).

Fear of Jeopardizing Patient's Survival in Case of Disease Progression Affects Adjuvant Treatment Recommendation

Thirty three percent (n=118) of respondents believe that survival outcomes are jeopardized if a patient's testicular seminoma progresses and/or metastasizes in the absence of adjuvant therapy and strict observation protocol. Among these 118 respondents, only 5% recommend observation as an adjuvant treatment for an otherwise healthy and compliant man with a small testicular seminoma, compared to 26% who recommend RT and 69% who recommend chemotherapy. There was a significant association between higher self-rated perceived depth of knowledge in the field of testicular seminoma and believing that survival is not jeopardized in case of testicular seminoma progression (p=0.03).

Clinical Factors (Tumor Size, Rete Testis, History of Prior Pelvic Surgery) Influence Treatment Recommendations

Sixty percent of respondents take into consideration tumor size and rete testis invasion when they recommend adjuvant treatment (Table-3). Recent graduates were more likely not to consider these clinical factors in their decision than physicians with more years of clinical experience (p=0.008), and there was a trend towards foregoing these considerations with increased self-reported knowledge (p=0.059). Consideration of these clinical factors was not associated with practice setting or the number of testicular seminoma patients evaluated or treated with RT.

Table 1 - Characteristics of radiation oncologists who completed the survey.

	Number of respondents (%)
Number of years after completion of residency training	
Currently in residency training	10 (2.83%)
0-2	15 (4.25%)
3-5	26 (7.37%)
6-10	48 (13.60%)
over 10	254 (71.95%)
Number of testicular seminoma patients evaluated over the past 12 months	
0	113 (32.01%)
<5	215 (60.91%)
5-10	18 (5.10%)
>10	7 (1.98%)
Number of testicular seminoma patients treated with RT over the past 12 months	
0	188 (53.25%)
<5	155 (43.91%)
5-10	7 (1.98%)
>10	3 (0.85%)
Practice setting	
Academic Center	128 (36.26%)
Private Practice	225 (63.74%)
Practice region	
Northern	81 (22.95%)
Pacific	62 (17.56%)
Southern	71 (20.11%)
Western	40 (11.33%)
Central	85 (24.08%)
Others/Unknown	12 (3.40%)
Canada	2 (0.57%)
Self-assessed depth of knowledge in the field of testicular seminoma	
Not comfortable evaluating patients	14 (3.97%)
Comfortable evaluating, but not an expert	257 (72.80%)
Expert in this field	82 (23.23%)

Table 2 - Adjuvant treatment recommendations for patients with stage i testicular seminoma.

	Adjuvant Treatment Type Recommended % (N)		
	Observation	Radiation Therapy	Chemotherapy
For a young patient with small pure seminoma (N=353)	84% (296)	10% (34)	6% (23)
For a patient who is judged to be poorly compliant (N=296)	3% (21)	67% (197)	30% (89)
For a patient with pure seminoma but persistently elevated markers after orchiectomy (Stage IS) (N=353)	7% (26)	28% (100)	64% (227)

Figure 1 - Perceived rate of noncompliance with clinical follow-up for patients with Stage I testicular seminoma among US radiation oncologists.

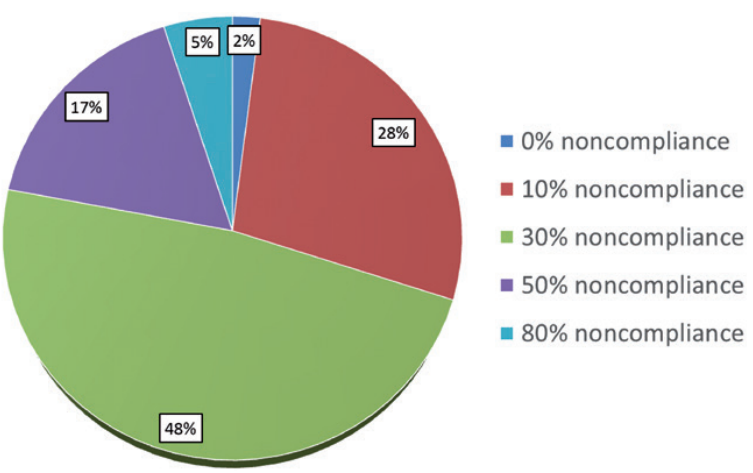

Table 3 - Influence of clinical factors on treatment recommendation.

Clinical Factor	Number of respondents (%)
Tumor Size and Rete Testis Invasion	
Affects treatment recommendation	211 (60%)
Does not affect treatment recommendation	142 (40%)
History of prior pelvic surgery	
Affects treatment recommendation	149 (42%)
Does not affect treatment recommendation	204 (58%)

42% (149) take into consideration history of prior pelvic surgery. Among these 149 respondents, for a patient with a history of prior pelvic surgery, only 10% recommend observation, whereas 41% recommend adjuvant chemotherapy and 49% recommend adjuvant RT.

Elevated Markers (Stage IS) Affect Treatment Recommendations

Only 7% (N=26) of respondents recommend observation for patients with elevated markers post-orchiectomy (Stage IS), whereas 28% recommend adjuvant RT and 64% recommend adjuvant chemotherapy (Table-2). Among these 26 respondents who support observation for Stage IS, 77% do not believe that disease progression or metastases jeopardize survival outcome in patients with testicular seminoma. When physicians were asked whether they would be ready to administer RT to a patient desiring this adjuvant treatment modality in the setting of pure seminoma by pathology but elevated pre-orchiectomy AFP levels, 44% of respondents supported the use of RT. There were no statistically significant associations between agreeing or refusing to offer adjuvant RT to patients with elevated AFP levels and self-described level of experience, number of seminoma patients evaluated or treated, or number of years beyond residency training. Practice setting was associated with treatment decision, with 64% of academic physicians and 51% of private practice practitioners refusing adjuvant RT with elevated AFP levels (p=0.02).

DISCUSSION

Adjuvant Treatment Recommendations

A recently published National Cancer Data Base analysis showed a dramatic change in management of patients with Stage I testicular seminoma between 1998 and 2011 in the US - with observation rates increased from 24% to 54%, while adjuvant RT rates decreased from 70% to 30% over these years (5). A previous survey of practicing radiation oncologists in US conducted in 2010 revealed only 20% of respondents recommending observation, with 60% recommending adjuvant RT and 3% recommending adjuvant chemotherapy. Our survey reveals contemporary patterns of care and provides basis for evaluating the practice change over the course of the last 6 years in the United States, with an overwhelming support for observation (84%) among radiation oncologists for compliant patients with no adverse features, such as large tumor size, rete testis invasion, history of prior pelvic radiation, or post-orchiectomy elevated tumor markers. This is an important victory for evidence-based practice, as several large prospective population-based studies revealed no difference in overall survival outcomes in patients treated with adjuvant therapies or observed clinically (2, 3), largely based on availability of highly efficacious salvage therapies. Moreover, a randomized trial MRC TE19/EORTC 30982 of carboplatin vs. radiation therapy with a median follow-up of over 6 years revealed no difference in relapse-free survival, and adjuvant chemotherapy resulted in a dramatic reduction in the rate of contralateral germ cell tumor development (HR 0.2) (7). For physicians concerned with disease progression in patients with stage I testicular seminoma, adjuvant chemotherapy could therefore be considered an excellent, if not superior, alternative to adjuvant RT. In fact, based on the results of a prospective population-based study in Norway and Sweden, radiation therapy has been completely abandoned as a treatment option for patients with Stage I seminoma in these countries, largely due to an increasing burden of proof of late radiation-induced secondary malignancies (8-10). Because Scandinavian oncologists are both radiation and medical oncologists by training and practice-and since diagnostic, treatment, and follow-up procedures are virtually free of charge to patients-this important healthcare decision appears to be based on clinical considerations rather than any economic incentives. In our survey radiation oncologists in private practice are more likely to recommend adjuvant RT than their colleagues in academic centers (13% vs. 3%, p=0.003), suggesting there is either less of an economic incentive in academic centers, or a better coordination of multi-disciplinary care that leads to more evidence-based patient-centered management recommendations.

Fears that drive radiation oncologists away from observation

Unfortunately, our survey results show that observation as a preferred management option is quickly dismissed when logistical or clinical features make patients with Stage I testicular seminoma appear to be less than desirable candidates for observation. Perceived noncompliance with observation protocol is one of the main concerns among US radiation oncologists. Seventy-six percent of our respondents have correctly identified the rate of noncompliance in the general population (10-30%), as supported by published reports (11). If a patient is perceived to be noncompliant, 67% of radiation oncologists recommend RT, 30% recommend chemotherapy, and only 10% continue to recommend observation. This dramatic change in recommendation can only in part be explained by fear of jeopardizing patient survival if disease recurrence is not detected early due to poor compliance, as only 33% of our respondents hold this view. The preference for adjuvant treatments in this scenario is not evidence based, as outcomes were shown to be similar among testicular cancer patients with good and poor compliances (12, 13). Moreover, 70% of our respondents do not believe that disease progression affects patient's outcomes, as salvage treatments are highly effective, bringing survival rates even among patients with metastatic seminoma into high 90 percent rates. In a large population-based analysis of patterns of relapse in men with Stage I testicular seminoma managed with active surveillance, 99% of relapses exhibited good-risk features, and all recurrences were cured with standard therapies (14). The fear of worse outcomes is less common among self-rated experts, so physician education is necessary to alleviate this fear among providers. But there may be an entrenched teaching among US radiation oncologists based on earlier guidelines and high profile manuscripts that suggested compliance should be an important consideration in patient evaluation and management decision (15). The time may have come to re-evaluate these dogmas and update contemporary teaching materials. Likewise, clinical factors, such as tumor size and rete testis invasion, have been previously considered prognostic factors for disease relapse and suggested to be incorporated in the treatment decision regarding adjuvant treatment, based on multi-institutional data published in 2002 (16). However, this analysis was updated in 2015 and revealed that rete testis invasion was no longer an independent factor, and the tumor cut-off size could no longer be used in the prognostic model for relapse. The authors concluded that the use of risk-adapted therapy based on the model incorporating tumor size and rete testis invasion was not recommended in clinical practice (17). Among our respondents 60% still routinely base their treatment recommendations on the presence of these two clinical factors. Another 40% of respondents take into consideration the history of prior pelvic surgery. Even though one could argue that the surgical disruption of tissue planes may alter the lymphatic drainage and hence lead to an altered pattern of disease spread, there is no evidence or rational explanation for potentially increased risk of disease recurrence on observation due to prior pelvic surgery. More education is necessary to dispel fears of increased disease progression among physicians and patients and empower patients not to fear disease recurrence due to highly effective treatment options available in the salvage setting.

Management of Stage IS Testicular Seminoma

Patients with elevated markers post-orchiectomy have Stage IS disease. This clinical scenario is not common, accounting for less than 5% of all patients with Stage I testicular seminoma based on NCDB analysis (5, 18). The best management option for these patients is unknown, since radiotherapy-based clinical trials have always excluded these patients (19), as did the randomized trial of chemotherapy vs. RT (7). It is also unclear from population-based analyses which management option results in the optimal long-term outcomes for patients with Stage IS testicular seminoma (18, 20). Current NCCN guidelines recommend repeating elevated serum tumor markers, assessing with abdominal/pelvic CT scan for evaluable disease, and treating according to extent of disease at relapse, rather than offering these patients adjuvant treatment in the absence of a clearly visible disease target (4). This is in stark contrast to our survey results, which reveal that 64% of respondents recom-

mend adjuvant chemotherapy, 28% adjuvant RT, and only 7% observation. An even less common scenario-but one that occasionally confuses both patients and physicians-is when pathology reveals pure seminoma but pre-orchiectomy alpha fetal protein (AFP) levels are elevated. Among our responders 44% were comfortable administering adjuvant RT. It is important to realize that elevated AFP is a hallmark of a non-seminoma germ cell tumor, and adjuvant RT is an inappropriate management in this clinical scenario.

Limitations

The greatest limitation of our study is a low response rate with a sample size of 353 evaluable responses. Our findings have to be interpreted with great caution, as they may not be representative of other radiation oncologists who chose not to participate in the survey. Very few respondents evaluated 5 or more patients with testicular seminoma in the span of a year, however, almost a quarter considered themselves experts in this field. This dichotomy is likely explained by decrease in referral of these patients to radiation oncologists in the United States.

CONCLUSIONS

There is a dramatic increase in acceptance of observation among US radiation oncologists treating patients with Stage I testicular seminoma. Our survey highlights fears and misconceptions among practicing US radiation oncologists that impede a wider adoption of observation strategy, revealing a dire need for educational outreach to minimize unnecessary treatments and reduce treatment-related toxicity among patients with Stage I testicular seminoma.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Can preoperative neutrophil lymphocyte ratio predict malignancy in patients undergoing partial nephrectomy because of renal mass?

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ABSTRACT

Purpose: To evaluate the importance of preoperative neutrophil lymphocyte ratio (NLR) predicting malignancy in patients who undergo partial nephrectomy due to renal mass.
Materials and Methods: Seventy nine patients who underwent open partial nephrectomy for renal masses were included in this retrospective study. In preoperative routine blood tests, renal ultrasonography and contrast-enhanced computed tomography were performed for all patients. Preoperative neutrophil lymphocyte ratio were compared in patients with clear cell renal cell carcinoma (Group1, 65 patients) and benign lesions (Group 2, 14 patients). The predictive ability of NLR was analyzed by ROC curves and Youden Index method was used to identify the cut-off value for NLR.
Results: The mean age of patients was 59.8±11.7 years in Group1 and 57.4±12.6 years in Group 2 (p=0.493). The mean tumor size was 3.8±1.2 cm in Group 1 and 3.3±1.0 cm in Group 2 (p=0.07). The median NLR was 2.48 (1.04) in Group 1 and 1.63 (0.96) in Group 2 (p<0.001). The area under a ROC curve was 0.799 (p<0.001).
Conclusions: Preoperative neutrophil lymphocyte ratio may predict renal masses that can not be distinguished radiologically. Our results must be confirmed by large and properly designed prospective, randomized trials.

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Carcinoma, Renal Cell; Neutrophils; Lymphocytes

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INTRODUCTION

Renal cell carcinoma (RCC) represents 2-3% of all cancers (1), with the highest incidence in Western countries. Over the last two decades until recently, the incidence of RCC increased by about 2% both worldwide and in Europe, although a continuing decrease has been observed in Denmark and Sweden (2). In 2012, there were approximately 84.400 new cases of RCC and 34.700 kidney cancer-related deaths in the European Union (3). In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilized or declined thereafter (4). Due to increased detection of tumors by ultrasound (US) and computed tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumors are usually smaller and of lower stage (5-7).

The relation between inflammation and tumor development and progression has been recognized in recent decades (8, 9). As a typical representative of inflammatory reactions, C-reactive protein (CRP) has been reported to be significantly associated with the prognosis of several cancers (10-14). Other systematic in-

flammation markers have been validated as predictive in various types of cancer (15-17).

The neutrophil to lymphocyte ratio (NLR) is also a widely used inflammatory marker that is defined as the absolute neutrophil count divided by the absolute lymphocyte count, and can be easily determined from complete blood cell parameters (18).

Unfortunately, radiological methods are still not sufficient for predicting malignancy. This can lead to unnecessary surgery in patients with benign renal masses. In this study, we investigated the importance of preoperative neutrophil lymphocyte ratio predicting malignancy in undistinguished radiological renal masses. This is the first study in the literature.

MATERIALS AND METHODS

Seventy nine patients who underwent open partial nephrectomy for renal masses were included in the study between 2006 and 2015. Patient data were analyzed retrospectively. In preoperative routine blood tests, renal ultrasonography and contrast-enhanced computed tomography were performed in all patients. NLR was compared in patients with clear cell RCC (Group 1, 65 patients) and benign lesions (Group 2, 14 patients). The predictive ability of NLR was analyzed by ROC curves and Youden Index method was used to identify the cut-off value for NLR.

Statistical Method

Normality distribution was investigated for all numeric variables. Categorical variables were described by frequencies and percentages and numeric variables were described by means and standard deviations or medians and interquartile ranges. The relationship between two categorical variables was tested by Chi-square test. Two independent means was compared by Student t test and two independent medians were compared by Mann Whitney U test. The predictive ability of NLR was analyzed by ROC curves and Youden Index method was used to identify the cut-off value for NLR. A p value less than 05 was accepted as statistically significant.

RESULTS

Mean age of patients was 59.8±11.7 years in Group 1 and 57.4±12.6 years in Group 2 (p=0.493). Mean tumor size was 3.8±1.2cm in Group 1 and 3.3±1.0cm in Group 2 (p=0.07). The median NLR was 2.48 (1.04) in group 1 and 1.63 (0.96) in group 2 (p<0.001). Both groups were similar in terms of sex and tumor side (Table-1) 14 patients had benign lesions. Eight patients had oncocytoma, 3 patients had calcified cyst, 2 patients had osseous metaplasia and 1 patient had angiomyolipoma.

Forty three (66.2%) of 65 patients had pT1a tumor and 22 (33.8%) of 65 patients had pT1b tumor 15 patients had grade 1 tumor, 46 patients had grade 2 tumor and 4 patients had grade 3 tumor. Optimal cut-off value of NLR was 1.725, with sensitivity of 93.8% and specificity 64.3% (Table-2).

The area under the ROC curve was 0.799 (p<0.001) (Figure-1). Predictive probability of NLR for tumor stage and grade were statistically insignificant (p=0.852) (Figures 2 and 3).

DISCUSSION

Increasing evidences support the involvement of systemic inflammation in cancer development and progression (9). It has been shown that, among the leukocytes in circulation, neutrophils increase and lymphocytes decrease as a systemic inflammatory response develops against the tumor. NLR has been used as an indicator of systemic inflammatory response (18).

An elevated NLR reflects both a decreased lymphocyte mediated antitumor immune response and a increased neutrophil dependent inflammatory reaction. Both of these factors may contribute to aggressive tumor biology, cancer progression, and poor prognosis (19, 20).

Despite recent progress in the identification of genetic, epigenetic and common molecular alterations in RCC (21), routine diagnostic and prognostic assessment of RCC currently relies on pathological tissue examination and traditional clinicopathological prognostic variables (22). The complexity of these molecular changes, as well as

Table 1 - Descriptive characteristics of the patients.

	Group 1 (n=65)	Group 2 (n=14)	p
Age(Mean±SD)	59.8±11.7	57.4±12.6	0.493
Sex(n, %)			
Male	35 (53.8)	6 (42.9)	0.455
Female	30 (46.2)	8 (57.1)	
Side(n, %)			
Right	35 (53.8)	7 (50)	0.794
Left	30 (46.2)	7 (50)	
Size (cm)(Mean±SD)	3.8±1.2	3.3±1.0	0.077
NLR(Median, IQR)	2.48 (1.04)	1.63 (0.96)	<0.001

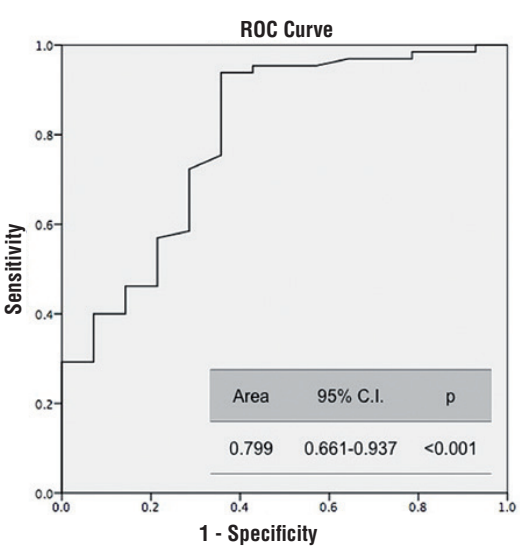
RCC = Renal cell carcinoma; **SD =** Standard deviation; **IQR =** Interquartile range

Table 2 - Cut-off values of NLR for malignancy.

	Cut-off values	Sensitivity %	Specificity %
Optimal	1.725	93.8	64.3
Max Sensitivity	1.275	100	7.1
Max Specificity	3.035	29.2	100

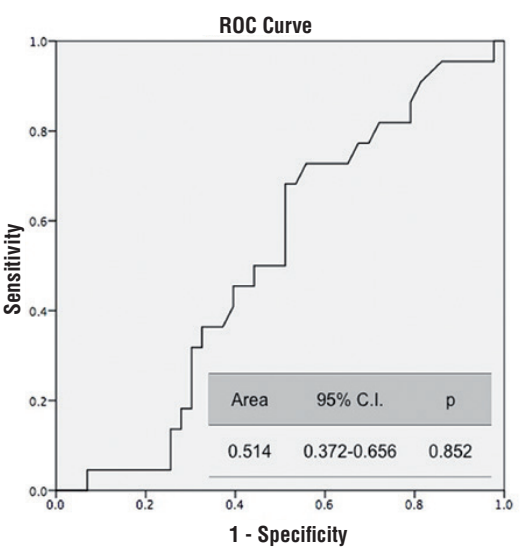
NLR = neutrophil lymphocyte ratio

Figure 1 - NLR predictive probability of the malignancy.



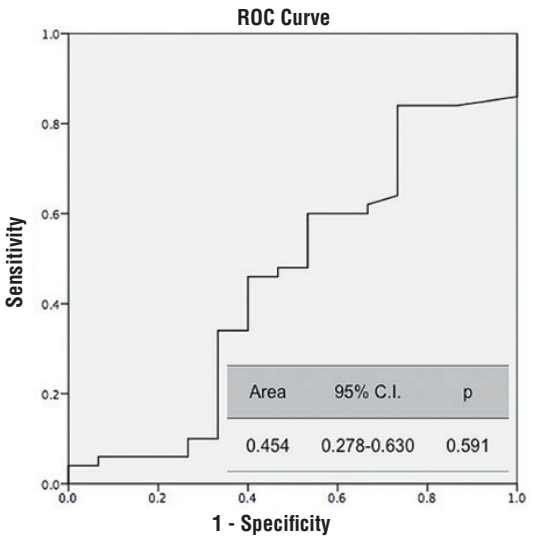
NLR = neutrophil lymphocyte ratio

Figure 2 - NLR predictive probability of tumor stage.



NLR = neutrophil lymphocyte ratio

Figure 3 - NLR predictive probability of the tumor grade.



NLR = neutrophil lymphocyte ratio

high costs of analyses, time-consuming preparation required and lack of evidence demonstrating how these newly discovered molecular markers influence diagnostic or therapeutic decisions, have rendered none of the markers available for routine testing.

Recently, several serum biomarkers and hematological indices representative of inflammatory response, notably C reactive protein (CRP), fibrinogen, lymphocyte-monocyte ratio, neutrophil--lymphocyte ratio (NLR) and platelet-lymphocyte ratio, have been demonstrated to be closely related to poor prognosis of patients with RCC (23-25). Therefore, NLR, defined as neutrophil counts divided by lymphocyte counts, is particularly noteworthy. Emerging evidences demonstrated that NLR showed its prognostic value in patients with colorectal cancer (26) and hepatocellular carcinoma (27). Patients with RCC with elevated levels of pretreatment NLR may be more likely to present a poorer clinical outcome (28).

There are other laboratory markers of systemic inflammation reaction besides NLR, such as CRP (29) and modified Glasgow prognostic score (30, 31), with a prognostic role in patients with RCC. Also, gene polymorphisms (32) and biological markers (33, 34) are suggested to be predictors of prognosis in patients with RCC. Although NLR is easy to measure, conditions such as active infection, inflammatory diseases, smoking behavior or stress at the time of blood collection may affect it (35).

In previous studies, it was demonstrated a relationship between poor prognosis and NLR. Unlike previous studies, we investigated the role of NLR in the malign-benign distinction. In the present study, we found that preoperative neutrophil lymphocyte ratio may predict renal masses that cannot be distinguished radiologically.

This study has several limitations. First, the study was retrospective. Second, NLR could be affected by different conditions, especially undetected diseases such as chronic infection, chronic disease, and autoimmune disorders, such as rheumatic disease. Third, the number of patients was especially low in the benign group. Our results should be confirmed by prospective randomized studies with large population patients. If confirmed, preoperative NLR will be an important tool to prevent unnecessary surgeries.

CONCLUSIONS

Preoperative neutrophil lymphocyte ratio might predict renal masses that cannot be distinguished radiologically. Our results must be confirmed by large and properly designed prospective, randomized trials.

CONFLICT OF INTEREST

None declared.

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Comparison of perioperative outcomes with or without renorrhaphy during open partial nephrectomy: A propensity score-matched analysis

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ABSTRACT

Purpose: Renorrhaphy in partial nephrectomy may damage intraparenchymal vessels and compress the renal parenchyma, which may lead to the formation of renal artery pseudoaneurysms or vascularized parenchymal volume reduction. Using propensity score matching, we compared surgical outcomes following non-renorrhaphy and renorrhaphy techniques for open partial nephrectomy (OPN) for T1a renal tumors.

Materials and Methods: We retrospectively analyzed data from 159 patients with normal contralateral kidneys who underwent OPN for T1a renal tumors and pre- and postoperative enhanced computed tomography between 2012 and 2015. Patient variables were adjusted using 1:1 propensity score matching between the two Groups: renorrhaphy (inner and outer layer sutures) and non-renorrhaphy (inner layer sutures only). Postoperative complications and renal function were compared between the two groups.

Results: We matched 43 patients per Group. Operative time, estimated blood loss, cold ischemic time, and postoperative hospital stay were not significantly different between the two Groups. Urine leakage (Clavien-Dindo grade ≥3) occurred in 0 renorrhaphy cases and 2 non-renorrhaphy cases (0% versus 4.6%, P=0.49). Renal artery pseudoaneurysm (RAP) occurred in 6 renorrhaphy cases and in 0 non-renorrhaphy cases (13% versus 0%, P=0.02).

Conclusions: The non-renorrhaphy technique may result in a lower risk of RAP but a greater risk of urine leakage. This technique needs further refinement to become a standard procedure for OPN.

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INTRODUCTION

Partial nephrectomy is the standard of care for small renal masses. In terms of oncological outcomes, partial nephrectomy is comparable to radical nephrectomy for such tumors. Partial nephrectomy is recommended to preserve renal function, which leads to the prevention of end-stage renal disease and cardiovascular events, and subsequently, the extension of patient survival (1-3). To prevent postoperative loss of renal function, a short ischemia time and the preservation of effective renal parenchyma are important. During surgery, many surgeons have contrived new techniques to reduce warm ischemia time, such as the early unclamping technique, zero ischemia technique, and selective renal artery clamping (4-6). To preserve the effective renal parenchyma, minimal margin resection and minimal renorrhaphy are necessary because the renal parenchyma will be compressed

by the sutures; in addition, renal blood flow will be reduced. In order to minimize the influence on renal function, various techniques, including the sliding clip technique, V-hilar suture, and non--bolstered horizontal mattress suturing, have been presented (7-10). However, with blind parenchymal suturing, intraparenchymal vessels may be injured, which may cause renal artery pseudoaneurysm (RAP) after surgery (11). At our institution, we have used a non-renorrhaphy technique for open partial nephrectomy (OPN) procedures since 2012 based on the idea that it preserves the effective renal parenchyma and prevents postoperative RAP. In the present study, we aimed to evaluate the preservation rate of renal functional outcomes and the postoperative complication rate of the non-renorrhaphy technique in OPN.

MATERIALS AND METHODS

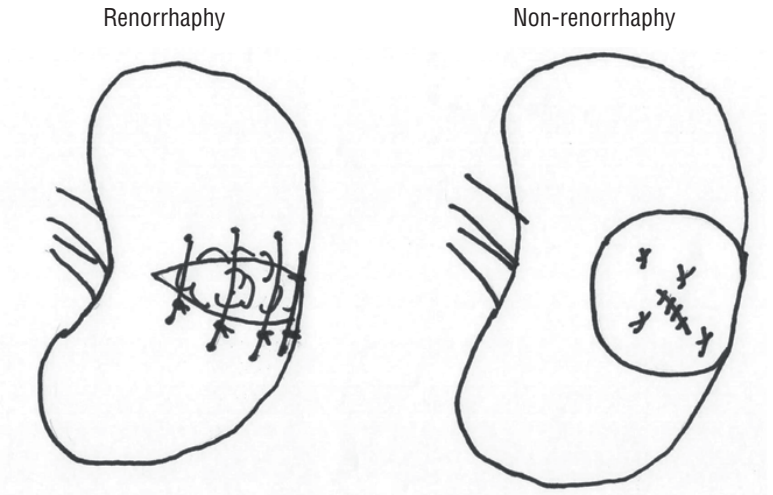
Institutional review board approval was obtained to retrospectively analyze patient data. A total of 167 patients underwent OPN for T1a renal tumors at a single institution between 2012 and 2015. The surgeries were primarily performed by three experienced surgeons. Of these cases, patients whose follow-up time and outcome data were available were included in the study. Patients who had an anatomically or functionally solitary kidney or those who could not undergo enhanced computed tomography (CT) because of allergic reaction or impaired renal function were excluded.

In 2012, we elected to carry out an institutional review board-approved CT study after partial nephrectomy for all patients who had no relative or absolute contraindications to the administration of intravenous contrast. In total, 158 patients were eligible for the study. The following variables were considered for each patient: age, sex, height, body weight, presence of hypertension (HT) or diabetes mellitus (DM), tumor diameter, RENAL nephrometry score, pre-and postoperative renal function, operating time, estimated blood loss, cold ischemia time (CIT), and incidence of complications, including RAP and urine leakage. Renal function was assessed using the estimated glomerular filtration rate (eGFR) before and 3 months after surgery. eGFR was calculated using the Modification of Diet in Renal Disease 2 equation (MDRD2) modified for Japanese patients as outlined by The Japanese Society of Nephrology (eGFR=1.94×serum creatinine mg/dL$^{1.094}$×age×0.739 [if female]) (12).

In the renorrhaphy technique, a retroperitoneal approach was made with flank incision. The renal artery and vein were clamped en bloc at the renal hilum. After 5 minutes of cooling with ice slush, the tumor was resected with 2–5 mm of the parenchymal margin; the transected vessels were ligated with 4-0 absorbable sutures and the opened collecting system was repaired with 4-0 absorbable sutures. The renal parenchyma was coagulated with monopolar coagulation (SOFT COAG, VIO 300D; ERBE Elektromedizin, Tubingen, Germany), avoiding the renal hilum, and parenchymal repair was performed with blind 1-0 absorbable interrupted sutures (1-2cm pitch and width) with oxidized cellulose (Surgicel; Ethicon Inc., Somerville, NJ, USA) stuffed in the parenchymal defect. In the non-renorrhaphy technique, parenchymal repair with blind 1-0 absorbable interrupted sutures was omitted; a Tachosil tissue--sealing sheet (CSL Behring Japan, Tokyo, Japan) was placed in the resected bed and manually compressed for 5 minutes after unclamping the renal hilum (Figure-1). To simplify the procedure, we do not routinely use intraoperative indigotindisulfonate injection through an ipsilateral ureteral catheter. If there was no urine leak or RAP upon contrast-enhanced CT angiography (CTA) on postoperative day 3, the drain was removed and patients were discharged. Urine leakage was defined as persistent drain output more than 48 hours after partial nephrectomy with a chemical analysis consistent with urine (13).

To minimize selection bias between patients who underwent renorrhaphy or non-renorrhaphy, patient variables, including age, sex, height, body weight, presence of HT or DM, tumor diameter, RENAL nephrometry score (4–12), and preoperative eGFR, were adjusted using 1:1 propensity score matching. Postoperative outcomes were then compared between patients with and without renorrhaphy in OPN. All statistical analyses were done with JMP 11 (SAS Institute, Cary, NC, USA). Propensity scores were calculated using

Figure 1 - The illustration of the renorrhaphy and non-renorrhaphy technique.



a multivariable logistic regression model by nearest-neighbor matching with a caliber of 0.2. The Student t test was used for continuous variables. The chi-squared test was used to estimate unordered categorical variables, and the Mann-Whitney U test was used to adjust for ordinal categorical variables.

$P < 0.05$ was considered statistically significant.

RESULTS

Table-1 lists pre-and post-matching patient characteristics. Forty-nine patients underwent OPN with renorrhaphy and 109 patients underwent OPN with non-renorrhaphy. Height, body weight, and presence of HT were significantly different between the two Groups. After adjusting for patient variables using 1:1 propensity score matching, we matched 43 patients per Group. After matching, the mean age was 58.6 (range, 27-82) years mean tumor size 28.9 (range, 10-40) mm and the mean preoperative eGFR was 64 (standard deviation (SD) ±19) mL/min/1.73m^2. The RENAL nephrometry score distribution of the entire matched cohort was as follows: low complexity (score 4-6), 19 (22%); intermediate complexity (score 7-9), 52 (60%); and high complexity (score 10-12), 15 (17%).

As listed in Table-2, there was no significant difference in mean operative time, estimated blood loss, CIT, or length of postoperative hospital stay between the matched Groups. As a postoperative complication, we compared the incidence of urine leakage and RAP. Urine leakage occurred in nine non-renorrhaphy cases and in one renorrhaphy case (20% [9/43] versus 2.3% [1/43], respectively, P=0.02), although there was no significant difference in the incidence of Clavien-Dindo grade ≥3 urine leakage between non-renorrhaphy and renorrhaphy cases (4.6% versus 0%, P=0.49). On the other hand, RAP occurred in six renorrhaphy cases but in zero non-renorrhaphy cases (13% [6/43] versus 0% [0/43], respectively, P=0.02).

In the pre-matched cohorts, 19 patients developed urinary fistula (one with renorrhaphy and 18 without renorrhaphy); one patient without renorrhaphy required transcutaneous drainage 5 weeks after surgery, six patients required ureteral stent drainage, and the other 12 patients did not require additional treatment.

RAP was detected using contrast-enhanced CTA 3 days after surgery; all asymptomatic RAP cases were prophylactically treated with transcatheter arterial embolization (TAE) according to another ongoing clinical study protocol, and none of the cases presented postoperative bleeding. Three months after surgery, there was no significant difference in postoperative eGFR (mL/min/1.73m^2) between the two Groups (56 versus 61, P= 0.23), but the decreasing rate of eGFR was

Table 1 - Characteristics of patients undergoing open partial nephrectomy pre- and post-matching.

	Pre-matching			Post-matching		
	Renorrhaphy	Non-renorrhaphy	P-value	Renorrhaphy	Non-renorrhaphy	P-value
No. of cases	49	109		43	43	
Age, years (range)	57 (31-80)	58 (27-82)	0.75	59 (33-80)	59 (27-82)	0.96
Sex (male/female)	34/15	73/36	0.85	30/13	32/11	0.63
Height, cm	166 (±7.3)	164 (±9.0)	0.03	166 (±7.4)	166 (±8.3)	0.91
Body weight, kg	67 (±12)	63 (±12)	0.04	65 (±11)	68 (±12)	0.81
No. of HT (%)	30 (61)	43 (39)	0.01	24 (55)	24 (55)	1.0
No. of DM (%)	12 (24)	22 (20)	0.53	10 (23)	8 (18)	0.59
Tumor size, mm (range)	28 (8-39)	30 (12-40)	0.30	28 (10-40)	29 (12-40)	0.84
Preoperative eGFR, mL/min/1.73 m^2	66 (±17)	65 (±19)	0.91	64 (±17)	63 (±18)	0.73
Nephrometry score median (IQR)	8 (6-9)	9 (7-9)	0.12	8 (7-9)	8 (7-9)	0.84
R	1 (1-1)	1 (1-1)	0.19	1 (1-1)	1 (1-1)	0.56
E	2 (1-3)	2 (2-3)	0.55	2 (1-3)	2 (2-3)	0.76
N	2 (2-3)	2 (2-3)	0.22	3 (2-3)	3 (2-3)	0.87
A a/x/p	18/22/9	37/45/27	0.88	16/18/9	15/17/11	0.65
L	2 (1-3)	3 (2-3)	0.23	3 (2-3)	3 (2-3)	0.89

Data are presented as mean (±standard deviation)

IQR = interquartile range; **HT =** hypertension; **DM =** diabetes mellitus; **eGFR =** estimated glomerular filtration rate; **R =** radius; **E =** exophytic/endophytic properties; **N =** nearness of the tumor to the collecting system or sinus; **A =** anterior/neither/posterior; **L =** location relative to the polar lines

significantly less in the non-renorrhaphy Group than in the renorrhaphy Group (-12%versus -2.2%, P=0.008).

DISCUSSION

The results of the present study comparing the incidence of complications demonstrate that the non-renorrhaphy technique in OPN resulted in a lower incidence of asymptomatic RAP and a higher incidence of urinary leakage, although the incidence of Clavien-Dindo grade ≥3 urine leakage did not differ significantly. At our institution, we adopted the non-renorrhaphy technique to reduce the occurrence of postoperative complications, including bleeding, hematoma, and RAP based on the hypothesis that blind large needle outer sutures used in the renorrhaphy technique could damage the intraparenchymal vessels. Actually, our results show that the incidence of vascular complication was higher in the renorrhaphy technique.

Renorrhaphy during OPN is considered one of the challenging parts of the procedure, as it requires tension to be applied with careful consideration of force and angle. Endress et al. studied the optimal tension of the parenchymal suture using fresh porcine kidneys and found that tension causing suture failure was only slightly higher than the tension typically applied during partial nephrectomy, and the

Table 2 - Comparison of surgical outcomes.

	Post-matching		
	Renorrhaphy (n=43)	Non-renorrhaphy (n=43)	P-value
Operative time, min	194 (±43)	191 (±39)	0.72
Estimated blood loss, mL	175 (±282)	143 (±205)	0.54
Cold ischemia time, min	43 (±19)	38 (±18)	0.69
No. of positive surgical margin	0	1 (2.3%)	0.47
No. of urine leaks (%)			
All	1 (2.3)	9 (20)	0.02
Clavien grade ≥ 3	0	2 (4.6)	0.49
No. of asymptomatic RAP (%)	6 (13)	0 (0)	0.02
Postoperative hospital stay, days	7.0 (±3.3)	6.0 (±2.4)	0.15
Postoperative eGFR (3 months later)	56 (±19)	61 (±19)	0.23
Postoperative decrease rate in eGFR, %	-12 (±20)	-2.2 (±13)	0.008

Data are shown as mean (±standard deviation); **RAP =** renal artery pseudoaneurysm; **eGFR =** estimated glomerular filtration rate.

acute angles of entry or exit are also likely to cause suture failure (14, 15).

Few reports detailing non-renorrhaphy techniques have been published. Ota et al. reported an initial series of 39 OPNs performed without renorrhaphy. Their outcomes were good, with preservation of postoperative renal function and prevention of urological complications. We began using a non-renorrhaphy technique for OPN in 2012, and have already completed 181 cases. We have already reported the surgical outcomes of non-renorrhaphy cases for T1b renal tumors (11). Forty-one patients underwent OPN without renorrhaphy for tumors >T1b. We evaluated renal function using eGFR and performed a volumetric analysis of vascularized parenchyma before and after the surgery; there was no benefit in terms of preservation of vascularized parenchymal mass for the operated kidney and eGFR compared to that in 50 patients who had undergone renorrhaphy. Regarding postoperative complications, the incidence of urinary fistula tended to be higher, but there was no significant difference between the two Groups. In the present study, the percent decrease in eGFR was higher in the renorrhaphy Group. However, this study did not include renal scintigraphy of the operated kidney and so may not be sufficient to conclude the superiority of the non-renorrhaphy technique for preserving renal function (11).

RAP is a life-threatening complication after partial nephrectomy, and the incidence of delayed hemorrhage from RAP after surgery is reported to range from 1.2 to 7.5% (16, 17). According to the institutional protocol and the approval of the institutional review board, we have routinely performed contrast-enhanced CTA for the screening of asymptomatic RAP in the early postoperative period, and have performed TAE for the prevention of delayed hemorrhage. In our previous study on the incidence of RAP after partial nephrectomy between January 2012 and May 2014, out of 212 cases in which postoperative CTA was not performed, delayed hemorrhage occurred in 10 (4.7%) cases. On the other hand, asymptomatic RAP was detected in 46 (15%) out of 312

cases, which was higher than the rate previously reported for symptomatic RAP. Prophylactic TAE was performed in 26 cases (8%) if the diameter of RAP was >5mm. As a result, delayed hemorrhage occurred in 2 cases (0.6%). We could reduce the incidence of delayed hemorrhage by performing prophylactic TAE for asymptomatic RAP (P=0.005) (18).

The mechanism of RAP development after partial nephrectomy has not been identified, but some possible causes have been reported, such as inadequate hemostasis of arterial bleeding from the resected bed, or injury of the renal vessels due to suturing with large needles in renorrhaphy (19-21). We previously reported that the risk of developing RAP was associated with the renal sinus exposure of renal tumors (22). Blind suture of the parenchyma with large needles has a higher potential to damage large vessels, especially when sutures are placed close to the renal sinus where the segmental arteries run. In the present study, we showed a lower incidence of asymptomatic RAP when using the non-renorrhaphy technique, which is consistent with this hypothesis. There are some concerns about the use of CTA in the early postoperative period for screening because of the adverse effects of contrast materials on renal function and because of radiation exposure. We have already published 4 papers regarding the early use of CTA, and have discussed how the advantages of the early detection of RAP to prevent rupture outweigh these safety concerns (18, 21-23). Our previous study also showed no significant difference in the decrease of eGFR with or without CTA in the early postoperative period (18, 21). Additional radiation exposure may increase the risk of secondary malignancy, but RAP rupture can make patients hemodynamically unstable and require emergent TAE and management in intensive care units. Comparing these risks, prioritization of the risk reduction by detecting asymptomatic RAP might offer greater advantages.

The incidence of urine leakage in OPN is reported to range from 1.0 to 17.4%; this incidence is higher than that in minimally invasive partial nephrectomy because of the indication for relatively hilar-located tumors in OPN (24). Urine leakage occurs if the collecting system opens during the resection of hilar tumors and is not fully repaired. In our study, the incidence of urine leakage was higher for patients undergoing non-renorrhaphy because of the lack of parenchymal packing with renorrhaphy. When using the renorrhaphy technique even a small collecting system opening, if left unrepaired, would be packed with renal parenchyma. In the present study, the incidence of urine leakage requiring additional treatment (Clavien-Dindo grade ≥3) was not significant. This result might be due to the detection of a small amount of urine leakage, which might have healed spontaneously due to the routine early postoperative CTA at our institution. Therefore, we assume that the differences in the incidence of urine leakage were not clinically important.

This study has several limitations, including its retrospective nature, collection of data from a single institution, and small sample size. The surgical procedure, whether renorrhaphy or non-renorrhaphy, may change depending on the surgeon's intraoperative findings. Patients in the early years of this study underwent renorrhaphy more frequently, whereas those in the later years of the study underwent non-renorrhaphy more often. Moreover, we did not specifically evaluate the operated kidney's function using nuclear renal scans or a volumetric analysis. We evaluated postoperative renal function using global renal function (eGFR) and included only patients with normal contralateral kidneys. The inferiority of postoperative renal function in the renorrhaphy group compared to that in the non-renorrhaphy Group may have been affected by the greater number of TAEs performed because of the greater incidence of asymptomatic RAP in our data set. Therefore, the difference in the percent decrease in eGFR may not be sufficient to conclude the superiority of the non-renorrhaphy technique for preserving renal function. In the present study, patient and tumor characteristics were adjusted using 1:1 propensity score matching and the postoperative complications were compared; asymptomatic RAP was more likely in the renorrhaphy technique and urine leakage was more likely in the non-renorrhaphy technique. Partial nephrectomy is well indicated for T1a renal tumors, so the outcomes of the present study will greatly assist surgeons in deciding whether to use non-renorrhaphy techniques.

In conclusion, for patients with T1a renal tumors, the non-renorrhaphy technique has the advantage of reducing the incidence of asymptomatic RAP, whereas the incidence of urine leakage was higher than that in the renorrhaphy technique. In order to become a standard procedure for OPN, especially for endophytic tumors, surgeons should consider additional techniques to ensure collecting system closure, such as intravenous or ureteral stent intra-operative indigotindisulfonate injection.

ABBREVIATION

CIT = cold ischemia time
CT = computed tomography
CTA = computed tomography angiography
DM = diabetes mellitus
eGFR = estimated glomerular filtration rate
HT = hypertension
MDRD = Modification of Diet in Renal Disease
OPN = open partial nephrectomy
RAP = renal artery pseudoaneurysm
TAE = transarterial embolization

Ethical approval

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

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Positive surgical margins are predictors of local recurrence in conservative kidney surgery for pT1 tumors

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ABSTRACT

Objectives: The clinical significance of positive surgical margin (PSM) after a Nephron Sparing Surgery (NSS) is controversial. The aim of this study is to evaluate the association between PSM and the risk of disease recurrence in patients with pT1 kidney tumors who underwent NSS.

Materials and Methods: Retrospective cohort study. A total of 314 patients submitted to a NSS due to stage pT1 renal tumor between January 2010 and June 2015 were included. Recurrence-free survival was estimated. The Cox model was used to adjust the tumor size, histological grade, pathological stage, age, surgical margins and type of approach.

Results: Overall PSM was 6.3% (n=22). Recurrence was evidenced in 9.1% (n=2) of patients with PSM and 3.5% (n=10) for the group of negative surgical margin (NSM). The estimated local recurrence-free survival rate at 3 years was 96.4% (95% CI 91.9 to 100) for the NSM group and 87.8% (95% CI 71.9 to 100) for PSM group (p=0.02) with no difference in metastasis-free survival. The PSM and pathological high grade (Fuhrman grade III or IV) were independent predictors of local recurrence in the multivariate analysis (HR 12.9, 95%CI 1.8-94, p=0.011 / HR 38.3, 95%CI 3.1-467, p=0.004 respectively). Fuhrman grade proved to be predictor of distant recurrence (HR 8.1, 95%CI 1.6-39.7, p=0.011).

Conclusions: The PSM in pT1 renal tumors showed to have higher risk of local recurrence and thus, worse oncological prognosis.

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INTRODUCTION

The increase in cross-sectional imaging studies in the last decades has made possible early detection of renal tumors. These achievements have propelled the Nephron Sparing Surgery (NSS) as the gold standard in the treatment of Stage T1 renal tumors (1-3). Such procedures do not imply in a significant increase in the postoperative morbidity with some discussions about the oncological results. Although EORTC group published in 2011 level 1 evidence against NSS in terms of survival, limitations of the study (recognized even by authors) and other publications showed comparable outcomes between radical and conservative renal surgeries (4-6).

Minimally invasive surgical techniques has changed the treatment paradigm of patients with RCC stage T1. Literature is contradictive concerning the rate of positive surgical margins (PSM) considering the surgical approach. While some authors suggest that Laparoscopic Partial

Nephrectomy (LPN) and robot-assisted partial nephrectomy present higher rates of PSM in comparison to Open Partial Nephrectomy (OPN) (7) others deny such difference (8).

The aim of this study is to evaluate the association of PSM with local and distant recurrence and describe the clinical and pathological characteristics that can predict recurrence in those patients with PSM and clinical stage T1.

MATERIALS AND METHODS

This is a retrospective cohort study including patients with pT1 renal cell carcinoma that underwent NSS either by open or minimally invasive surgery (laparoscopic or robot-assisted), from January 2010 to June 2015 at the Hospital Italiano de Buenos Aires, Argentina. Three possible surgical techniques were used based on tumor location: enucleation (resection of the tumor only); polar nephrectomy (resection of the entire pole including single or multiple lesions) or hemi-nephrectomy (half of the kidney was resected including single or multiple lesions). Enucleation was the first choice whenever possible (exophytic lesions without sinus involvement). Minimally invasive and open NSS technique have been previously described (9, 10). Data was collected prospectively from the electronic clinical history. Demographic data and the clinical pathological characteristics as well as the follow-up registry were tabulated: gender, body mass index (BMI), tumor size, approach, histologic sub-classification, Fuhrman grade, PSM and clinical situation at the last follow-up (no recurrence, local recurrence, distant recurrence or death by cancer). Pathology exam data was detailed according to the sixth edition of the American Joint Committee on Cancer (AJCC) TNM (11). The nuclear grade was informed based on the Fuhrman classification (12). A computed tomography (CT) scan of the chest, abdomen and pelvis with intravenous contrast was performed for staging the tumor.

The surgical approach was registered (open, minimally invasive). All the resected pieces were revised by the same pathologist experienced in oncological urology. A positive margin was assigned to the tumor cell that contacted with chinese ink.

The oncologic follow-up was performed according to the NCCN guidelines (13).

Local recurrence was defined as a tumor mass in the ipsilateral kidney over the resection bed of the same histological type of the original tumor.

Patients older than 18 years of age with single renal tumors pT1a and pT1b with a minimum follow-up of three months were included.

Patients with multiple and/or bilateral tumors, metastases at the time of diagnosis, benign tumors or hereditary renal tumors (Von Hippel Lindau), were excluded.

The presence of PSM or NSM was registered. Both populations were compared and the oncologic results were analysed according to local or distant recurrence.

Statistical analysis

Continuous normally distributed variables are expressed by their mean and standard deviation. Not normally distributed variables are expressed as medians and their interquartile (IQR) ranges and categorical variables are expressed as n (%). To compare the continuous variables with normal distribution we used the T-test. In case of not normally distribution we utilized the Mann-Whitney test. To compare the categorical variables we used the Chi-square or Fisher test if the assumption for the first was not complied. For the estimation of disease-free survival (DFS) we used the method of Kaplan Meier expressed in estimated time and its confidence interval of 95% (95% CI). In the case of comparing subgroups, the log rank test was used. For the estimation of risk in the univariable or multivariable analysis, we used the Cox regression, expressing the hazard ratio (HR) and 95% CI. In Cox multivariable models, cases with not informed Fuhrman grade were dropped. To avoid collinearity with stage (more important for us), we did not include tumor diameter in multivariable analysis. Statistical significance was considered to be at $p<0.05$. Analyses were performed using SPSS 18.0®.

The present study was approved by the Institutional Ethics Committee after the protocol's revision and the procedures used according to international regulations (CEPI 3028).

RESULTS

In the period between January 2010 and June 2015, 347 NSS surgeries were performed in patients with pT1. Of all the studied patients, 314 met the inclusion criteria. There were 22 PSM (9 open, 12 laparoscopic and 1 robot-assisted), the rate of PSM for open, laparoscopic and robotic assisted approach was 6.3%, 5% and 7.9%, respectively (p=0.673). Table-1 shows no difference in baseline characteristics between groups by margin status. The minimally invasive approach was used in 172 (54.8%) patients, 20 of which were operated with robotic assistance. Clear cell carcinoma was the most common histologic type followed by chromophobe and papillary with no statistical difference in PSM (6.1%, 11.1%, and 10% respectively, p=0.79). The median follow-up was 24 months (IQR 12-40).

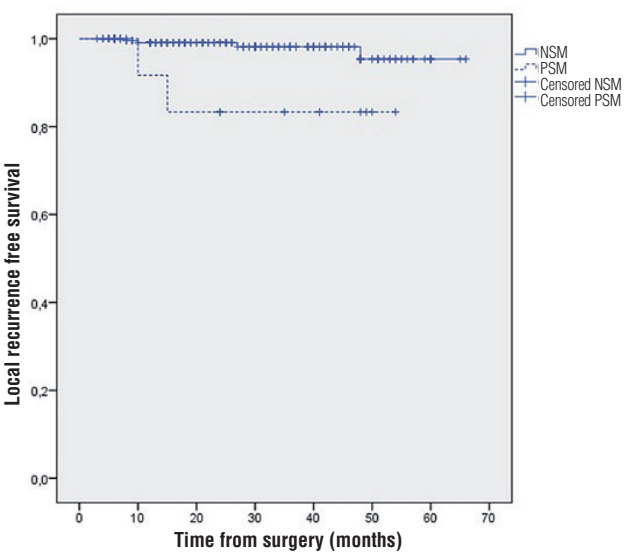
During follow-up, local recurrence rate was 1.9% (6 patients). In PSM group we found 2 (9.1%) local recurrences both with synchronic distant metastases. In the NSM group there were 4 local recurrences (1.4%), 2 with synchronic distant metastases. Six patients, all in the NSM group, presented with distant metastases alone.

Table 1 - Baseline characteristics.

	Total	NSM	PSM	p
No. pts (%)	314	292 (93)	22 (7)	
Male (%)	218 (69.4)	202 (69.2)	16 (72.7)	0.72
Mean Age (SD)	58.3 (12)	58.2 (12.2)	58.9 (14.8)	0.81
Mean BMI (SD)	28.2 (4.8)	28.2 (4.7)	28.6 (4.8)	0.67
Approach (%)				**0.67**
Open	142 (45.2)	133 (45.5)	9 (40.9)	
Minimally Invasive	172 (54.8)	159 (54.5)	13 (59.1)	
Median tumor size mm (IQR)	29.7 (21-38)	30 (21.2-38)	27 (20-30)	0.51
Histology (%)				**0.92**
Clear-cell	245 (78)	230 (78.8)	15 (68.2)	
Chromophobe	45 (14.3)	40 (13.7)	5 (22.7)	
Papillary type I	10 (3.2)	9 (3.1)	1 (4.5)	
Papillary type II	10 (3.2)	9 (3.1)	1 (4.5)	
Other	4 (1.3)	4 (1.3)	0 (0)	
Fuhrman (%)				**0.62**
Non informed	49 (15.6)	44 (15.1)	5 (22.3)	
Grade I y II	258 (82.2)	242 (82.9)	16 (72.7)	
Grade III y IV	7 (2.2)	6 (2)	1 (4.5)	
Tumor Stage (%)				**0.82**
pT1a	266 (84.7)	247 (84.6)	19 (86.4)	
pT1b	48 (15.3)	45 (15.4)	3 (13.6)	

The estimated local recurrence-free survival (LRFS) rate at 3 years for the NSM group was 96.4% (CI 91.9-100), while for the PSM group was 87.8% (95% CI 71.9-100), with a statistically significant difference (log rank test p=0.02; Figure-1). The estimated metastasis-free survival (MFS) rate at 3 years in patients with PSM was 87.8% (95% CI 71.9-100) and for those who had NSM was 95.4% (95% CI .92, 1-98.7), with no significant difference (p=0.127 log rank test). Only 1 patient died of disease progression at 12 months (pT1b, Fuhrman II, NSM).

Figure 1 - Local recurrence free survival by margin status.



The estimated 3 year LRFS and MFS for Fuhrman III-IV was 66.7% and 50% respectively, in contrast to 98.1% and 95.2% in Fuhrman I-II (p=0.0001).

PSM and Fuhrman grade III or IV were independent predictors of LRFS, while stage, age, tumor size and type of approach didn't result as predictors (Table-2). High Fuhrman grade and tumor stage were the only factors that increased the risk of metastases (Table-3). For multivariable analysis, cases without Fuhrman informed (i.e., chromophobe) were dropped out, thus cohort analysed included 265 patients.

The presence of local recurrence in the univari able analysis shows an increased risk of distant recurrence with a HR 33.4 (95% CI 9.3-119, p=0.0001).

The PSM rate for group Fuhrman I-II and III-IV was 6.2% and 14.3%, respectively with no positive association (p=0.367).

DISCUSSION

Trends in NSS are rising around the world, although there are some concerns about the significance of PSM in terms of oncological outcomes (14, 15). Nowadays incidental renal tumors are frequently found and suitable for NSS (16, 17). In this study, we evaluated the association between PSM and local or distant recurrence in patients with pT1 renal tumors undergoing NSS.

Several studies highlight the impact of PSM on recurrence free survival (14, 15, 18-27). Shah et al. recently reported in a large retrospective cohort of patients undergoing partial nephrectomy for localized renal tumors, that some patients with high risk disease (eg pT2-pT3a or Fuhrman grade II-III) with PSM will experience relapse with distant metastasis (28). As well as some authors (22, 28) we found that PSM was independently associated with local recurrence, but not directly linked with distant recurrence. This relationship was observed in higher Fuhrman grade (III and IV), but we didn´t demonstrated increased risk in T1b tumors (over T1a). We didn´t analyse histological type because our high prevalence of clear cell histology.

A multicentric retrospective study comparing 111 patients with PSM and 664 patients with NSM, concluded that patients with PSM presented a higher risk of local recurrence, even though there were no statistically significant differences in recurrence-free survival, cancer-specific survival and overall survival (14). In relation to this work, the Memorial Sloan Kettering Cancer Center (20) analysed 777 PN between 1989 and 2005. Of 75 patients who had PSM (7.5%), only 2 developed local recurrence (4%), while from 713 patients (92; 5%) with NSM, 4 presented recurrence (0.5%). They concluded that patients with PSM have a higher incidence of local recurrence, not determined by the margin status. A bibliographic review of 3.803 RCC and 173 PSM concluded that

Table 2 - Univariable and multivariable analysis of local recurrence.

	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
PSM	7.3 (1.33-40.2)	0.023	7.7 (1.3-47)	0.026
Age	1.01 (0.94-1.08)	0.718	1.02 (0.9-1.1)	0.601
Tumor size mm	1.01 (0.94-1.08)	0.701	++	++
Fuhrman				
Grade I-II	Ref.		Ref.	
Grade III-IV	20.3 (3.7-110)	0.001	16.3 (1.9-135)	0.01
Stage				
pT1a	Ref.		Ref.	
pT1b	2.5 (0.47-13.9)	0.28	0.8 (0.1-7.7)	0.861
Approach				
Laparoscopic	Ref.		Ref.	
Open	0.4 (0.08-2.5)	0.36	0.5 (0.08-4.1)	0.578

++ Excluded to avoid collinearity with Stage.

Table 3 - Univariable and multivariable analysis of distant recurrence.

	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
PSM	3.7 (0.8-17.7)	0.09	3.5 (0.7-17)	0.127
Age	1.03 (0.9-1.1)	0.305	1.03 (0.9-1.1)	0.266
Tumor size mm	1.08 (1.04-1.14)	0.0001	++	++
Fuhrman				
Grade I-II	Ref.		Ref	
Grade III-IV	19.5 (5-75.8)	0.001	9.4 (2.1-43)	0.004
Stage				
pT1a	Ref.		Ref.	
pT1b	8.23 (2.3-29.2)	0.001	5.2 (1.2-22)	0.026
Approach				
Laparoscopic	Ref.		Ref.	
Open	0.35 (0.09-1.3)	0.129	0.9 (0.2-4.4)	0.902

++ Excluded to avoid collinearity with Stage

a positive margin in PN rarely correlates with local recurrence (15, 20-23). Khalifeh et al. (24) published a total of 943 robot-assisted PNs; 21 patients (2.2%) had PSM and 922 had NSM. When comparing both groups, they concluded that PSM had higher rates of local recurrence and metastases ($p<0.001$) in relation to NSM and that there was a statistically significant difference in the recurrence-free survival and metastasis between the two groups (log rank test <0.001). PSM presented 18.4 more times the risk for recurrence in the multivariate study. Patients with PSM present worse oncological prognosis, higher probabilities of local recurrence of the disease (log rank test $p=0.02$) and perhaps more likely to have distant recurrence (although without significant difference, log rank test $p=0.127$). An interesting fact is that local recurrence increases the risk of metastasis (HR 33.4), which highlights the importance of determining the risk of local recurrence itself.

It is debatable to analyse recurrence without inform cancer specific survival that is the principal global oncologic outcome, even with PSM. Reports that underestimate the value of PSM, may incur in a bias in the truly effect of PSM in cancer survival.

It is controversial what to do with PSM. Although the American Urological Association and the National Comprehensive Cancer Network guidelines do not recognize the clinical significance of PSM, in view of our results it seems reasonable to follow-up all patients but with close surveillance imaging (28). Nephrectomy or repeat resection remains unnecessary with no study demonstrating clear advantages. Several studies observed that PSM not necessarily signify residual disease. Benalash et al. observed residual disease in only 39% of patients with PSM who underwent repeat surgery (14).

In agreement with other authors, we found that the rate of positive margins is comparable between open and minimally invasive surgery, for the path does not predispose to risk of recurrence (27, 29).

Although we have not routinely performed intra-operative frozen sections, its relevance grows as a PSM seems to impact in local relapse. Unfortunately, many authors suggest that intraoperative frozen section has limited utility. Arguments against the routine use of frozen section in NSS, are that it has a relatively high false-negative rate and inconsistency in changing intra-operative management (30).

This study presents some limitations. It is a retrospective study of a single center, so the results could be sensitive to selection bias. The low incidence of positive surgical margins and the relative infrequency of pathologically aggressive lesions treated with NSS explain the low number of events that lead us to wide HR confidence intervals that may limit the interpretations of our findings, despite significance, so caution must be taken in the results interpretation. On the other hand, finding this level of increased risk with this number of events is unlikely to happen by chance bias.

Based on the outcomes of uni/multivariable analysis and Kaplan Meier curves adjusted by grade and PSM, recurrences are more likely to happen in the first two years and not proportional with time, but follow-up is too short to ensure the proportional model.

CONCLUSIONS

PSM in NSS for pT1 tumors has a lower local recurrence-free estimated survival compared to patients with NSM. Fuhrman grade is another predictor of disease free survival. The relationship between PSM and Fuhrman grade should be studied to ensure that the complete resection of the tumor should not be underestimated. However, larger series of patients and longer follow-up time is needed to draw more accurate conclusions.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Synchronous abdominal tumors: is combined laparoscopic surgery in a single approach a safe option?

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ABSTRACT

Background and Purpose: Recent advances in cancer treatment have resulted in better prognosis with impact on patient's survival, allowing an increase in incidence of a second primary neoplasm. The development of minimally invasive surgery has provided similar outcomes in comparison to open surgery with potentially less morbidity. Consequently, this technique has been used as a safe option to simultaneously treat synchronous abdominal malignancies during a single operating room visit. The objective of this study is to describe the experience of two tertiary cancer hospitals in Brazil, in the minimally invasive treatment of synchronous abdominal neoplasms and to evaluate its feasibility and peri-operative results.

Materials and Methods: We retrospectively reviewed the data from patients who were submitted to combined laparoscopic procedures performed in two tertiary hospitals in Brazil from May 2009 to February 2015.

Results: A total of 12 patients (9 males and 3 females) with a mean age of 58.83 years (range: 33 to 76 years) underwent combined laparoscopic surgeries for the treatment of at least one urological disease. The total average duration of surgery was 339.8 minutes (range: 210 to 480 min). The average amount of intraoperative bleeding was 276.6mL (range: 70 to 550mL) and length of hospitalization was 5.08 days (range: 3 to 10 days). Two patients suffered minor complications regarding Clavien system during the immediate postoperative period.

Conclusions: Combined laparoscopic surgery for the treatment of synchronous tumors is feasible, viable and safe. In our study, there was a low risk of postoperative morbidity.

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Keywords:
Laparoscopy; Neoplasms; Neoplasms, Multiple Primary

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INTRODUCTION

Recent advances in cancer treatment have resulted in an improvement of prognosis with a profound impact in patient's survival (1). This fact, associated with the advances in technology and diagnostic methods, have led to an increase in the incidence of a second primary neoplasm. The published frequency of multiple malignancies is 1 to 3% according to international literature (1, 2). While diagnosis of synchronous primary tumors is relatively uncommon, their management warrants consideration. Experts prioritize the treatment of the most aggressive malignancy with the worst prognosis (3).

Surgical treatment of synchronous tumors of the same histologic origin has been routinely performed in many oncologic scenarios (1-4). Usually, it consists in extraction of a primary tumor and a solitary metastasis, as in colon cancer. A systematic review published in 2009 showed that, in selected cases, patients with a colon primary tumor and synchronous liver metastasis could be treated by open surgery in a single procedure, instead of two surgeries as a sequential treatment, with the same feasibility and complication rates (4).

The benefits of minimally invasive treatment in contemporary urologic practice are well established. Similar oncologic outcomes are achieved in comparison to open surgery, however with potentially more desirable cosmetic results, less post-operative pain, shorter hospital stay, lower complication rates and earlier postoperative recovery (5-7). Since the first laparoscopic nephrectomy published by Clayman et al. in 1991 (8), there have been numerous technological developments that have allowed a wide adoption of minimally invasive procedures for the treatment of both benign and malign urologic diseases.

Because of the well tolerated minimally invasive surgical approach, performing simultaneous treatment of synchronous abdominal malignancies in a single procedure has been accepted by the international urological society (9). Due to the lack of extensive data on combined laparoscopic surgeries, current literature fails to demonstrate the perceived benefits and efficacy of this approach. The objective of this study is to describe the experience of two tertiary cancer hospitals in Brazil, in the minimally invasive treatment of synchronous abdominal neoplasms and to evaluate its feasibility and peri-operative results.

MATERIALS AND METHODS

We retrospectively reviewed the data from patients who underwent combined laparoscopic procedures performed in two tertiary hospitals in Brazil from May 2009 to February 2015. All Informed consents were applied before each surgery and were not repeated for data collection.

The inclusion criteria for the study group were as follows: (A) both procedures were performed laparoscopically under a single application of anesthesia; (B) at least one of the procedures was performed for the treatment of a urologic disease and (C) the procedures were in different sites of the abdomen, meaning two separate procedures. Specialists in oncology and minimally invasive surgery, in an inter-disciplinary approach, performed all the surgeries. The initial procedure was elected according to physician's decision and in agreement with both surgeons. All procedures were performed under general anesthesia. Bowel preparation was performed only for colorectal surgeries and antimicrobial prophylaxis for all procedures was done with a first-generation cephalosporin. In case of colorectal surgery, it was added metronidazole. Postoperative complications were described and classified according to the Clavien-Dindo Classification of Surgery Complications (10).

The data was obtained from patient records (emergency room data, visits and office) and patient demographics were recorded. Descriptive statistical analyses were made using the software IBM SPSS Statistics version 20. All ethical aspects of this manuscript were reviewed and approved by the Institution Review Board from both institutions.

RESULTS

A total of 12 patients: 9 males (75%) and 3 females (25%) with an average age of 58.83 years (range: 33 to 76 years) underwent combined laparoscopic surgery for the treatment of at least one urologic disease. The most common type of urologic surgery, which was performed on 10 patients, was to address a renal tumor (partial or radical nephrectomy and nephroureterectomy). Additionally, one patient underwent an adrenalectomy and one had a radical prostatectomy. The combined laparoscopic procedures consisted of 10 non-urological procedures (6 colectomies, 3 rectosigmoidectomies and 1 total gastrectomy), while 2 had synchronous urologic procedures (left nephroureterectomy with right partial adrenalectomy and left radical nephrectomy with right adrenalectomy). All the procedures performed and their respective pathological findings are listed in Table-1.

Table 1 - Pathological findings regarding urologic and non-urologic diseases.

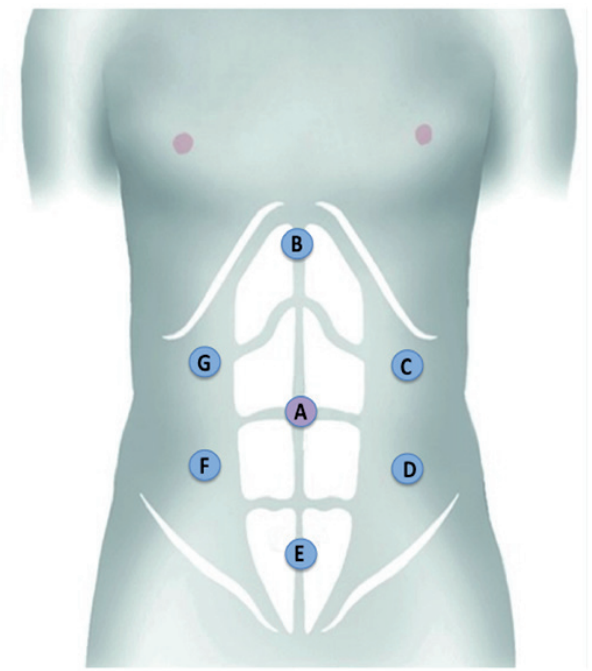
Patient	Pathology test Urological pathology	Pathology test Non-urological pathology
1	Anaplastic plasmacytoma	Anaplastic plasmacytoma
2	High grade urothelial carcinoma	Colon adenocarcinoma
3	Renal cell carcinoma (clear cells)	Moderately differentiated colon adenocarcinoma
4	Adenocarcinoma arising from tubulovillous adenoma	Metastatic adenocarcinoma (adrenal)
5	Renal cell carcinoma (clear cell)	Tubular adenocarcinoma of the rectum
6	Renal cell carcinoma (clear cell)	Mucinous gastric adenocarcinoma / chronic cholecystitis
7	Adenocarcinoma metastasis / poorly differentiated adenocarcinoma	Poorly differentiated adenocarcinoma
8	Renal oncocytoma	Rectum tubulovillous adenocarcinoma
9	Renal cell carcinoma (clear cell)	Adrenal carcinoma
10	Renal cell carcinoma (clear cell)	Colon Adenocarcinoma
11	Urothelial carcinoma	Adrenal adenoma
12	Prostate adenocarcinoma, Gleason 4+4	Well -differentiated adenocarcinoma

The mean duration of surgery was 339.8 minutes (range: 210 to 480 min.). The average amount of intraoperative bleeding was 276.6mL (range: 70 to 550mL). All procedures were performed using a trans-peritoneal approach with number of trocars varying from a minimum of 4 to a maximum of 6. The number of trocars utilized was minimized whenever possible and placement was coordinated between surgeons to accommodate their individual needs. The schematic figure provides the suggested port placement for all cases (Figure-1). The specimens were placed in a laparoscopic specimen bag and removed at the end of the procedure by Pfannenstiel, median infra umbilical or Gibson's incision, depending on patient position or surgeon's preferences. There were no intraoperative complications, no conversions to open surgery and no intraoperative mortalities in this group. The average length of hospitalization was 5.08 days (range: 3 to 10 days). Only two patients suffered complications during the 90 days postoperative period; one patient had a transitory hand paresthesia related to surgical positioning and the other one was diagnosed with nosocomial pneumonia and treated successfully with empirical antibiotics. Both complications were classified as Clavien II, and were considered minor. The remainder of patients experienced no complications during the 90 days postoperative period. Table-2 summarizes the demographic and intraoperative data.

DISCUSSION

The American Cancer Society has recently reported that 20% of Americans will develop cancer in their lifetime. Furthermore, for those patients who develop a tumor, the chance of developing a second tumor during their lifetime is around 30% (3). Specific to urologic cancers, the finding of a second primary tumor has been reported in the literature with an incidence range of 3.3 to 6.6% (11-14). A subset of these patients will develop two primary tumors synchronously, leaving the oncologists with a difficult dilemma: which tumor should be treated first (1-3)?

Figure 1 – Port Placement.



A – Used for camera in all cases Schematic Port placement (5, 10 and 12 mm).

A, B, C, D – case 6
A, B, C, D, G – case 9
A, C, D, F, G – cases 1, 2, 3, 4, 7, 10
A, C, D, E, F, G – cases 5, 8, 11, 12

In the urology field, the finding of a second primary tumor has been reported in the literature. Sugiyama et al. (11) found an incidence of multiple cancers in their patients with urologic cancer of 6.6%. In another study by Wegner et al. (12), over a 19-year period at the University of Berlin Hospital, there was a secondary tumor incidence of 3.3%. Nogueras-Gimeno et al. (13) and Mikata et al. (14), in two other studies, found an incidence of 6.1% and 6.4% of secondary tumors in their patients with urologic cancer, respectively.

Simultaneous open surgery has been described as a successful treatment option for other synchronous non-urological malignancies (4, 15). Hillings et al. (4) performed a meta-analysis of studies comparing combined versus staged resection of synchronous liver metastases from colorectal cancer, focusing on length of hospital stay, in-hospital morbidity, mortality and 5-year survival. The data analysis revealed that combined surgery may lead to a shorter length of hospitalization and less morbidity, but it does not seem to affect long-term survival, and in the early decade, at least, it had a larger 30-day mortality. Kim et al. (16) were one of the pioneers to demonstrate that patients with synchronous abdominal tumors could undergo laparoscopic surgery in a single procedure. In a series of 10 laparoscopically managed cases of metastatic colon cancer with liver implants, the results regarding intra and post-operative complications and length of hospitalization were comparable to published series that describe these procedures carried out separately (17).

With the advance of new technologies, laparoscopy became a safe and effective treatment option for various urological diseases with many potential benefits. Patients may experience a shorter hospitalization period, early postoperative recovery and better cosmetic results (9, 18). Therefore, specialists have sought to extend these benefits to combined laparoscopic procedures for the treatment of two or more diseases. This strategy has numerous advantages for patients such as: exposure to a single anesthesia; reduction of hospitalization; potential for decreased morbidity and postoperative pain due to smaller incisions; better cost-effectiveness. Smaller incisions may also contribute to the reduction of abdominal wall-related complications, such as evisceration and incisional hernias, which ultimately reduces costs due to the elimination of secondary procedures therefore minimizing psychological and surgery-related stress (7). Our study had a favorable complication rate of 16.6% (2 cases), both classified as grade 2 in Clavien-Dindo Classification of Surgery Complications, which is consistent with published literature (Table-3).

Laparoscopic surgery may also have some disadvantages in comparison to open surgery when evaluating synchronous surgeries. Hemodynamic changes secondary to prolonged pneumoperitoneum and specific patient positioning (for example, Trendelemburg position)

Table 2 - Demographic caractheristics, intraoperative data and complications.

Patient	Age (y)	Gender	Urologic Surgery performed	Non-urologic Surgery performed	Time (min.)	EBL (mL)	IOC	LOH days	POC
1	33	M	Left radical Nephrectomy	Total colectomy	350	150	No	6	No
2	75	F	Right radical nephrectomy	Left colectomy	470	400	No	7	No
3	55	M	Right radical nephrectomy	Right colectomy	210	200	No	3	No
4	74	F	Left adrenalectomy	Right colectomy	358	200	No	5	No
5	57	M	Right Partial Nephrectomy	Rectum amputation	360	550	No	4	No
6	76	M	Left radical nephrectomy	Subtotal gastrectomy + cholecystectomy	290	500	No	7	No
7	53	M	Right radical nephrectomy	Right hemicolectomy	300	70	No	3	No
8	53	M	Right Partial nephrectomy	Recto-sigmoidectomy	480	350	No	5	No
9	50	M	Left radical nephrectomy	Right adrenalectomy	250	150	No	2	No
10	60	F	Right Partial Nephrectomy	Right colectomy	370	200	No	5	No
11	65	M	Left Nephroureterectomy	Right partial adrenalectomy*	220	150	No	10	Yes
12	55	M	Radical Prostatectomy	Rectosigmoidectomy	420	400	No	4	Yes

IOC = intraoperative complications; **POC =** postoperative complications; **LOH =** Length of Hospitalization

Table 3 - Complications described in literature.

Author	Year	Main Surgery	Open / Lap	N	Clavien I (%)	Clavien II (%)	Clavien IIIa/b	Clavien IV	Total (%)
Inoue (15)	2014	Colorectal	Lap	10	-	2	-	-	2 (20)
Hillings (4)	2008	Colorectal	Open	641	NR	NR	NR	NR	224 (35)
Maurya (9)	2009	Urology	Lap	32	1(3.1)	4(12.5)	-	-	5(15.6)
Reisiger (30)	2005	Urology	Lap	13	1(7.7)	2(15.4)	2(15.4)	-	5(38.4)
Lin (17)	2015	Colorectal	Open	36	-	8 (22)	3 (8.5)	-	11(30.5)
			Lap	36	-	7 (19.4)	2 (5.5)	-	9 (24.9)
Cartapatti (present study)	2015	Urology	Lap	12	-	2 (16.6)	-	-	2 (16.6)

could become a limitation to this approach if surgery duration is prolonged. Meininger et al., in a prospective study, evaluated hemodynamic features with patients in the Trendelemburg position with the pneumoperitoneum set at 12mmHg during laparoscopic radical prostatectomy, demonstrating that the head-down position caused only a significant increase in central venous pressure, while the induction of pneumoperitoneum for a period of 4 hours significantly affected the mean arterial pressure. All other hemodynamic parameters remained nearly unaffected (19). Meininger et al. in another study published in 2006 compared overweight and non-obese patients regarding hemodynamics and gas exchange during laparoscopic radical prostatectomy and found severe impairment in oxygen exchange in the overweight group, with no impact in hemodynamics (20). Prolonged pneumoperitoneum can also affect oxidative stress as it raises the intra-abdominal pressure, producing significant organ ischemia followed by reperfusion injury on deflation of the abdomen. This so-called ischemia-reperfusion injury would be present at the end of a prolonged induced pneumoperitoneum and may lead to organ injury and failure (21, 22). Nonetheless, all reported changes were transitory with no permanent impairment in patient's renal or cardio-respiratory functions. Based on these considerations, laparoscopy can negatively impact on patients' health and therefore prolonged surgeries should be avoided, especially in patients with cardio-pulmonary morbidities or obesity. Nevertheless, experienced surgeons can reach acceptable operative time even in combined procedures (9).

Tsivian et al. (18) described 19 patients who underwent concomitant laparoscopic kidney surgery and cholecystectomy and reported an acceptable duration of surgery and hospitalization, in addition to the efficacy and safety of the procedure. Papalia et al. (5) described a series of 32 cases of patients who underwent combined laparoscopic surgery for the treatment of synchronous urological tumors and also found that the technique was feasible and safe, with an acceptable intraoperative duration and level of bleeding and no conversion to open surgery. Gill et al. (23) also described the safety, efficacy and viability of combined surgery in a group of patients with autosomal dominant polycystic kidney disease subjected to bilateral synchronous nephrectomy. When combined laparoscopic surgery involves non-urological diseases, it is important to include other specialists on the surgical team to reduce the duration of the procedure. Moreover, another factor that contributes to achieve this objective is the presence of experienced surgeons (16, 18).

Some authors have also reported cases of robotic-assisted combined laparoscopic surgery, with the same benefits as the combined laparoscopic procedures previously described (24-29). Another important aspect of combined laparoscopic surgery is that it is possible to use the same access sites for both procedures, adding at maximum another one or two entry sites (5, 30).

In tertiary services in countries such as Brazil, where the institution's financial problems sometimes may interfere in treatment election, a combined approach for synchronous pathologies might be a good solution. It seems only logical that one single surgery, minimizing disposable waste, minimizing the total anesthetic and pain medications used, while achieving similar hospitalization periods would be less expensive than the sequential approach. This hypothesis is not confirmed by this study, as analysis of cost--effectiveness was not part of our objectives. Further studies into the cost effectiveness and safety of simultaneous laparoscopic surgeries should be pursued.

CONCLUSIONS

Combined laparoscopic surgery for the treatment of at least one urological condition is a feasible, viable and safe choice. This approach provides acceptable intra- and postoperative morbidity, has the potential for shorter hospitalization, less anesthetic and pain medication usage, and may decrease recovery time. Because of these potential benefits, this approach can reduce costs and burden for patients. Due to the poten-

tial for prolonged operative time, we recommend that this approach should only be done in larger oncologic centers and by experienced surgeons to minimize the risks and optimize its benefits.

CONFLICT OF INTEREST

None declared.

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Vaginal cuff recurrence after radical cystectomy: an under – studied site of bladder cancer relapse

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ABSTRACT

Introduction: Vaginal cuff recurrence of tumor following radical cystectomy is a rare site of disease recurrence, however it has never been specifically studied. The aim of the study is to evaluate incidence, risk factors, and long-term oncologic outcomes of vaginal cuff recurrence in a cohort of female patients treated with radical cystectomy for invasive urothelial carcinoma of the bladder.

Materials and Methods: From 1985 to 2012, a prospectively maintained institutional bladder cancer registry was queried for vaginal cuff recurrence post radical cystectomy. Overall mortality and cancer-specific mortality were reported using the Kaplan-Meier method for patients with vaginal cuff recurrence, recurrence at another local or distant site, and those without evidence of recurrence. Comparisons were performed using the log-rank test. Cox proportional hazards regression model was performed to assess predictors of vaginal cuff recurrence.

Results: From 469 women treated with radical cystectomy for bladder cancer, 34 patients (7.3%) developed vaginal cuff recurrence, 130 patients (27.7%) had recurrence involving either a local or distant site, and 305 patients (65%) had no evidence of recurrence. The 5-year overall mortality-free survival rate was 32.4% for vaginal cuff recurrence, but 25.0% for other sites of recurrence. Cancer-specific mortality-free survival rate was 32.4% for vaginal cuff recurrence, and 30.3% for the other sites of recurrence. Multivariate Cox proportional hazards regression analysis demonstrated that the presence of tumor in posterior location at radical cystectomy (Hazard Ratio [HR], 0.353 [95% CI, 0.159-0.783]) and anterior vaginectomy, compared to no vaginectomy (HR, 2.595 [95% CI, 1.077-6.249]) were independently associated with vaginal cuff recurrence.

Conclusion: Anterior vaginectomy, despite our best attempts, is perhaps not sufficient to prevent vaginal cuff recurrence. Therefore, follow-up evaluation is essential, and further studies are necessary to address the optimal approach for initial management.

Patient Summary: Although vaginal cuff recurrence is an unusual site of recurrence, careful evaluation is needed before cystectomy and during follow-up to identify patients at risk.

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INTRODUCTION

Radical cystectomy with pelvic lymph node dissection is the gold standard for both muscle invasive bladder cancer, and high-risk non-muscle invasive bladder cancer (1). Female patients with aggressive disease can be treated with anterior pelvic exenteration, which includes cystectomy, bilateral

pelvic lymph node dissection, hysterectomy, bilateral salpingo-oophorectomy, and resection of the upper third of the anterior vaginal wall (2). Since local tumor extension may affect reproductive organs, anterior pelvic exenteration aims to achieve a balance between local cancer control and adequate sexual outcomes. However, it is not clear when the routine removal of reproductive organs is required to avoid local recurrence (3, 4). Recurrence after radical cystectomy is not unusual, with estimated 5-year recurrence rates of 30%-52% and cancer-specific mortality rates of 28%-35% (5-9).

The incidence of local invasion involving gynecological organs at the time of radical cystectomy ranges from between 2.7% to 7.5% in patients undergoing anterior pelvic exenteration (10-12). The vagina is the sexual organ most frequently found involved by bladder cancer, with an estimated frequency of 4.8% (13). However, vaginal cuff recurrence following radical cystectomy has never been specifically analyzed. A better understanding of this particular site of recurrence would indeed optimize female patient selection, counseling for reproductive organ preservation, and indication for orthotopic neobladder, with the purpose of improving quality of life and preserving sexual health. In response to these needs, our primary aim is to assess the incidence, overall survival, and cancer-specific survival rates for patients with vaginal cuff recurrence following radical cystectomy. The secondary aim is to identify possible independent predictors of bladder cancer recurrence in the vaginal cuff.

MATERIALS AND METHODS

Following institutional board review approval, a retrospective cohort study was conducted at Mayo Clinic. A prospectively maintained institutional bladder cancer registry was queried to identify women who underwent radical cystectomy for curative intent between 1985 and 2012, but had no evidence of metastatic bladder cancer. Exclusion criteria included known metastatic disease at surgery, incomplete follow-up data, and failure to provide research consent. Cystectomy usually involved anterior pelvic exenteration with removal of the bladder, cervix, uterus, and anterior vaginal wall. Anterior vaginectomy, defined as the removal of the anterior vaginal wall at the time of radical cystectomy, was performed in the presence of aggressive cancer with evidence of extravesical extension (cT3 and cT4 disease). Patients with a clinically resectable bladder tumor not involving the bladder neck, were considered candidates for an orthotopic urinary diversion. In order to achieve proper placement and support of neobladder, a urethral and vaginal sparing technique was performed. In all other cases, the urethra and external ostium of the uterus were removed. Sacrocolpopexy was not included as part of the radical cystectomy.

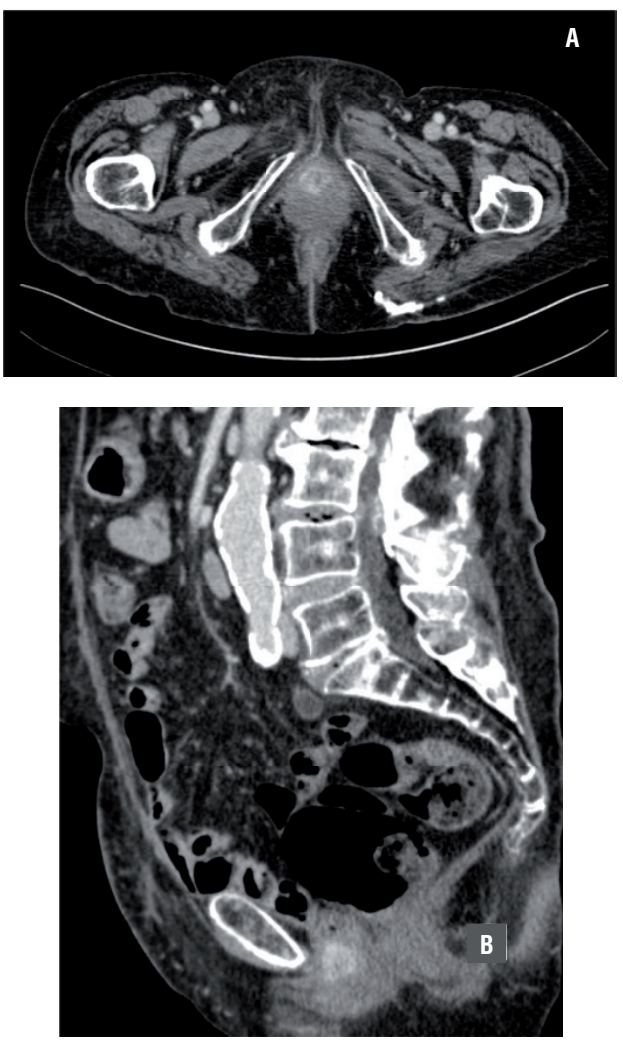
Owing to the retrospective nature of this study, post-operative surveillance after radical cystectomy was not standardized. However, at our institution, patients are typically followed every 3 months for the first two years after surgery, every 6 months for the subsequent two years, and then annually thereafter. Oncologic surveillance included history, physical examination, urine cytology, and radiologic imaging of the chest, abdomen, and pelvis.

Cancer recurrence was defined as evidence of bladder cancer on imaging after radical cystectomy (Figure-1), with or without the presence of symptoms. Radiographic studies included bone scintigraphy, positron emission tomography/computed tomography scan, computed tomography and magnetic resonance imaging. Biopsy confirmation of bladder cancer recurrence was performed in the presence of considerable diagnostic uncertainty. Clinical recurrences were categorized as either vaginal recurrence, or recurrence at another local, pelvic, or distant site. Vaginal cuff recurrence was defined as radiographic recurrence in the vaginal cul-de-sac invading the posterior vagina.

The date of recurrence was defined as the date of first positive imaging or positive biopsy for bladder cancer recurrence. Last follow-up date was the last date of visit or correspondence between the patient and the institution. Causes of death were identified from death certificates and physician correspondence. Bladder cancer was considered the cause of death when it was listed as the main or first cause. Data regarding administration of perioperative chemotherapy and radiation were also collected.

Frequencies and proportions were used to summarize categorical variables. Means, medians,

Figure 1 - Vaginal cuff recurrence in an 82 year old female. After undergoing radical cystectomy and lymphadenectomy (pT3aN0 tumor), patient subsequently developed symptomatic vaginal blood spotting. The CT scan demonstrates a solid mass originating from the vaginal cuff. Surgery was performed and final pathology showed a recurrence of urothelial carcinoma originating from the vaginal cuff.



and interquartile ranges were reported for continuously coded variables. The t test and χ^2 test were used to compare the statistical significance of differences in mean and proportions, respectively. Kaplan-Meier analyses were performed to evaluate overall mortality and cancer specific mortality-free survival rate after radical cystectomy for patients with vaginal cuff recurrence, patients with cancer recurrence at another site, and those without recurrence. Log-rank analyses were used to compare overall mortality and cancer specific mortality among the aforementioned groups. Multivariate Cox proportional hazards models were then used to assess independent predictors of vaginal cuff recurrence. The following variables were included in the multivariate model: orthotopic vs. ileal conduit, anterior vaginectomy, administration of perioperative chemotherapy, pathologic T stage (pT>2 vs. pT≤2), and bladder tumor location at radical cystectomy (anterior vs. posterior). Tumor in the posterior bladder wall, base, trigone, posterior urethra, and ureterovesical junction at radical cystectomy were described as posterior in location. All analyses were performed using the SAS statistical package (SAS Institute, Inc).

RESULTS

The study included 469 women with bladder cancer who received treatment with radical cystectomy. Vaginal cuff recurrence was detected in 34 patients (7.3%). Recurrence at other sites was identified in 130 patients (27.7%), and no recurrence occurred in 305 patients (65%). Tables 1 and 2 describe the baseline characteristics of patients with vaginal cuff recurrence, other sites of cancer recurrence and those without recurrence. The three study groups did not demonstrate significant differences with regards to the analyzed variables.

A significant difference was demonstrated when comparing overall mortality and cancer specific mortality-free rate between patients with vaginal cuff recurrence and patients without any recurrence (log-rank <0.001) (Figures 2a and 3a). The 5-year overall survival rate was 32.4% for patients with vaginal cuff recurrence and 25.0% for other sites of recurrence (Figure-2b). Cancer-specific survival rate was 32.4% for vaginal cuff recurrence and 30.3% for other site of recurrence (Figure-3b). No significant differences were found when comparing overall mortality and cancer specific mortality-free rates between those with vaginal cuff recurrence, and patients with recurrence at other sites (Log-Rank p=0.83 and 0.82, respectively).

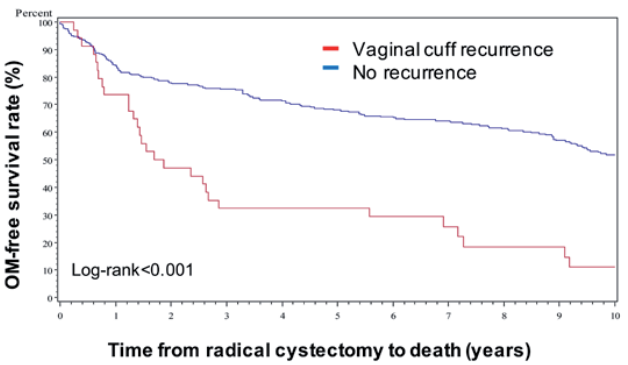
When univariate and multivariate Cox proportional hazards regression analysis compared vaginal cuff recurrence to recurrences at other sites, the presence of bladder cancer in the posterior

Table 1 - Distribution of Risk Factors Among Vaginal Cuff Recurrence (A) vs. Recurrence at Other Sites (B) vs. No Recurrence (C).

	Vaginal Cuff Recurrence	Recurrence at Other Sites	No Recurrence	*p* Value	*p* Value
	(n=34)	(n=130)	(n=305)	A vs B	A vs C
	(A)	(B)	(C)		
Age				0.2	0.5
Median(IQR)	70.5 (63-76)	68 (62-74)	69 (62-76)		
Decade				0.3	0.3
1980s	8 (23%)	37 (28%)	75 (25%)		
1990s	18 (53%)	50 (38%)	121 (40%)		
2000s	8 (23%)	43 (33%)	109 (36%)		
ECOG performance status				0.7	0.8
0	24 (71%)	98 (75%)	222 (73%)		
1	8 (23%)	22 (17%)	56 (18%)		
2	2 (6%)	8 (6%)	22 (7%)		
3	0	2 (1%)	5 (2%)		
BMI				0.5	0.2
BMI ≤25	12 (35%)	63 (48%)	149 (49%)		
BMI 26-30	14 (41%)	40 (31%)	100 (33%)		
BMI 31-35	7 (21%)	21 (16%)	36 (12%)		
BMI >35	1 (3%)	6 (5%)	20 (7%)		
Orthotopic urinary diversion	5 (15%)	20 (15%)	47 (15%)	0.9	0.9
pT					
≤pT2	18 (53%)	58 (45%)	189 (62%)	0.5	0.6
pT>2	16 (47%)	72 (55%)	116 (38%)		
pN				0.4	0.3
NX	2 (6%)	20 (15%)	50 (16%)		
N0	28 (82%)	87 (67%)	223 (73%)		
N1	1 (3%)	12 (9%)	15 (5%)		
N2	3 (9%)	10 (8%)	13 (4%)		
N3	0	1 (1%)	4 (1%)		
Lymph nodes at RC					
Positive	4 (12%)	23 (18%)	32 (10%)	0.4	0.8
Peripheral tumor margin	0	4 (3%)	5 (2%)	0.3	0.7
Perioperative chemotherapy	7 (21%)	21 (16%)	32 (10%)	0.5	0.1
Median Time to last follow-up among alive in years (IQR)	6.3 (6-19)	12.5 (9-26)	12.9 (8-17)	0.4	0.4
Smoker	19 (56%)	75 (58%)	178 (58%)	0.8	0.8
Prior pelvic radiation	1 (3%)	7 (5%)	178 (58%)	0.6	0.5
Multifocal tumor	0	11 (8.5%)	13 (4%)	0.1	0.2

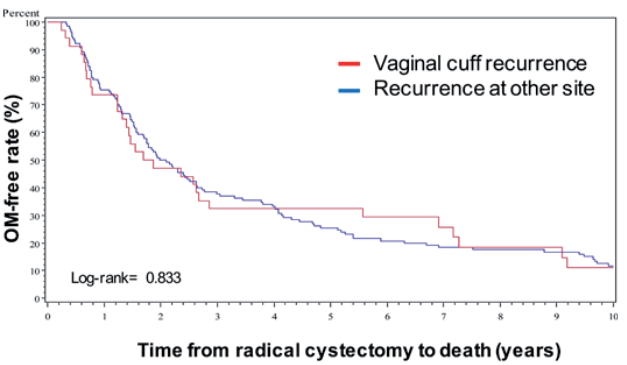
Figure 2 - Overall Mortality (OM) for Vaginal Cuff Recurrence vs No Recurrence (2a) and vs Recurrence at Other Site (2b).

A



Time to bladder cancer death/ last follow-up	Other Recurrence: Number at risk	Other Recurrence: Bladder cancer–free survival	Vaginal Recurrence: Number at risk	Vaginal Recurrence: Bladder cancer–free survival
1	255	0.842	25	0.735
5	202	0.68	11	0.324
10	127	0.519	3	0.11

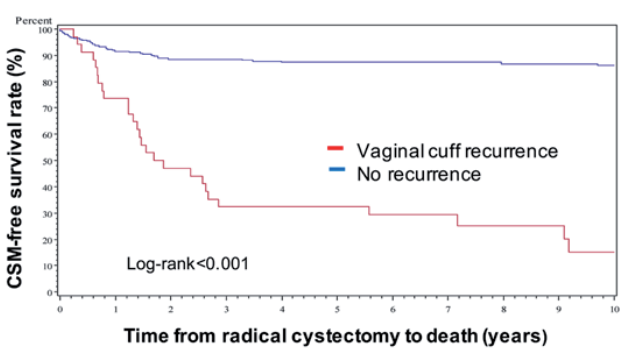
B



Time to bladder cancer death/last follow-up	Other Recurrence: Number at risk	Other Recurrence: Bladder cancer–free survival	Vaginal Cuff Recurrence: Number at risk	Vaginal Cuff Recurrence: Bladder cancer–free survival
1	98	0.754	25	0.735
5	33	0.254	11	0.324
10	14	0.117	3	0.11

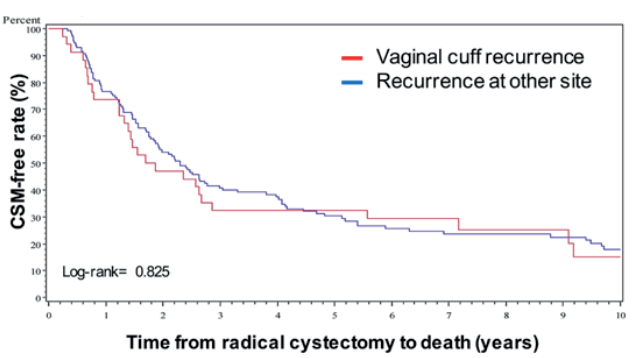
Figure 3 - Cancer Specific Mortality (CSM) for Vaginal Cuff Recurrence (3a) vs No Recurrence and vs Recurrence at Other Site (3b).

A



Time to bladder cancer death/last follow-up	Other Recurrence: Number at risk	Other Recurrence: Bladder cancer–free survival	Vaginal Cuff Recurrence: Number at risk	Vaginal Cuff Recurrence: Bladder cancer–free survival
1	255	0.915	25	0.735
5	202	0.873	11	0.324
10	127	0.861	3	0.151

B



Time to bladder cancer death/ last follow-up	Other Recurrence: Number at risk	Other Recurrence: Bladder cancer–free survival	Vaginal Cuff Recurrence: Number at risk	Vaginal Cuff Recurrence: Bladder cancer–free survival
1	98	0.766	25	0.735
5	33	0.303	11	0.324
10	14	0.179	3	0.151

floor was found to be independently associated with a lower risk of vaginal cuff recurrence (Hazard Ratio [HR], 0.346 [95% CI, 0.159-0.0104]; P=0.007) (Table-3). On multivariate analysis, anterior vaginectomy was independently associated with development of vaginal cuff recurrence (HR, 2.595 [95% CI 1.077-6.249]; P=0.03) (Table-3).

Treatment for recurrences were as follows: five (14.7%) patients underwent salvage surgery, 20 (76.4%) received adjuvant chemotherapy, and three (8.9%) patients were treated with palliative radiation therapy.

Table 2 - Distribution of Risk Factors Among Vaginal Cuff Recurrence vs No Recurrence.

	No Recurrence (n=305)	Vaginal Cuff Recurrence (n=34)	Total (N=339)	*P* Value
Age				0.49
N	305	34	339	
Mean (SD)	68.1 (10.9)	70.0 (8.2)	68.3 (10.7)	
Median	69	70.5	70	
Q1, Q3	62.0, 76.0	63.0, 76.0	62.0, 76.0	
Range	19.0-91.0	53.0-86.0	19.0-91.0	
Decade				0.27
1980s	75 (24.6%)	8 (23.5%)	83 (24.5%)	
1990s	121 (39.7%)	18 (52.9%)	139 (41.0%)	
2000s	109 (35.7%)	8 (23.5%)	117 (34.5%)	
ECOG performance status				0.78
0	222 (72.8%)	24 (70.6%)	246 (72.6%)	
1	56 (18.4%)	8 (23.5%)	64 (18.9%)	
2	22 (7.2%)	2 (5.9%)	24 (7.1%)	
3	5 (1.6%)	0 (0.0%)	5 (1.5%)	
BMI				0.23
Missing	1	0	1	
BMI≤25	148 (48.7%)	12 (35.3%)	160 (47.3%)	
BMI 26-30	100 (32.9%)	14 (41.2%)	114 (33.7%)	
BMI 31-35	36 (11.8%)	7 (20.6%)	43 (12.7%)	
BMI >35	20 (6.6%)	1 (2.9%)	21 (6.2%)	
Orthotopic urinary diversion				0.91
Missing	1	0	1	
0=No	257 (84.5%)	29 (85.3%)	286 (84.6%)	
1=Yes	47 (15.5%)	5 (14.7%)	52 (15.4%)	
pT				0.59
≤pT1	133 (43.6%)	13 (38.2%)	146 (43.1%)	
pT2	56 (18.4%)	5 (14.7%)	61 (18.0%)	
pT3/T4	116 (38.0%)	16 (47.1%)	132 (38.9%)	
pN				0.33
NX	50 (16.4%)	2 (5.9%)	52 (15.3%)	
N0	223 (73.1%)	28 (82.4%)	251 (74.0%)	
N1	15 (4.9%)	1 (2.9%)	16 (4.7%)	
N2	13 (4.3%)	3 (8.8%)	16 (4.7%)	
N3	4 (1.3%)	0 (0.0%)	4 (1.2%)	
Lymph nodes at RC				0.82
Negative	273 (89.5%)	30 (88.2%)	303 (89.4%)	
Positive	32 (10.5%)	4 (11.8%)	36 (10.6%)	
Peripheral tumor margin				0.67
No	298 (97.7%)	34 (100.0%)	332 (97.9%)	
Yes	5 (1.6%)	0 (0.0%)	5 (1.5%)	
Perioperative chemotherapy				0.08
No	273 (89.5%)	27 (79.4%)	300 (88.5%)	
Yes	32 (10.5%)	7 (20.6%)	39 (11.5%)	
Time to last follow-up				0.38
N	108	3	111	
Mean (SD)	13.8 (7.1)	10.3 (7.5)	13.7 (7.1)	
Median	12.9	6.3	12.8	
Q1, Q3	8.1, 17.4	5.7, 19.0	7.9, 17.5	
Range	0.0-32.6	5.7-19.0	0.0-32.6	
Smoker				0.78
Never	127 (41.6%)	15 (44.1%)	142 (41.9%)	
Yes	178 (58.4%)	19 (55.9%)	197 (58.1%)	
Prior pelvic radiation				0.48
No	287 (94.1%)	33 (97.1%)	320 (94.4%)	
Yes	18 (5.9%)	1 (2.9%)	19 (5.6%)	
Multifocal				0.22
No	292 (95.7%)	34 (100.0%)	326 (96.2%)	
Yes	13 (4.3%)	0 (0.0%)	13 (3.8%)	

Table 3 - Multivariate Association of Risk Factors with Vaginal Cuff Recurrence vs Recurrence at Other Site.

	Univariate				Multivariate			
Variables	HR estimate	95% CI for OR		P value	HR estimate	95% CI for OR		P value
Localization								**0.01**
Posterior	Ref.			0.01	Ref.			
Anterior	0.346	0.159	0.751		0.353	0.159	0.783	
Diversion								**0.99**
Incontinent	Ref.				Ref.			
Continent	1.117	0.388	3.218	0.84	0.991	0.303	3.242	
Vaginectomy								**0.03**
No	Ref.			0.07	Ref.			
Yes	2.011	0.934	4.329		2.595	1.077	6.249	
Perioperative chemotherapy								**0.28**
Yes	Ref.				Ref.			
No	1.346	0.519	3.492	0.54	1.811	0.620	5.295	
pT2 vs ≤pT1	0.629	0.197	2.007	0.68	0.587	0.170	2.030	**0.80**
pT3/T4 vs ≤pT1	0.615	0.267	1.417	0.53	0.460	0.181	1.172	**0.26**

CI = confidence interval; **OR =** odds ratio

DISCUSSION

Recurrence patterns of disease among women following radical cystectomy have been poorly described in the literature. Current guidelines marginally address the issue of sexual-sparing cystectomies in the female population. Women have been reported to experience worse cancer outcomes than men with locally advanced bladder tumors (14, 15). The etiology for this difference in outcome remains to be established, but is presumed to result from delayed presentation of disease, healthcare disparities (16), vesical anatomy, and different levels of sex hormones (17). The largest studies have defined recurrent bladder urothelial carcinoma as the presence of recurrent cancer within the soft tissue field of surgical resection, without particular attention to the differences in pelvic anatomy between males and females (15, 18-20). We believe, however, that a more precise study is crucial for treatment, prognosis and follow-up purposes.

In this context, we found a 7.3% incidence of vaginal cuff recurrence among women following radical cystectomy. In the current literature, a limited number of studies evaluate the involvement of reproductive organs at final radical cystectomy pathology. In particular, Ali-el-Dein et al. (12) estimated secondary malignant involvement of reproductive organs in female cystectomy specimens in 2.6% of cases. In another study, the vagina has been described as the most commonly involved reproductive organ at radical cystectomy, with an incidence of 4.8% (13). Our findings demonstrate a significant difference in both overall mortality and cancer specific mortality-free survival between patients with vaginal cuff recurrence and patients without recurrence. Interestingly, no survival differences were found between vaginal cuff recurrence and recurrence at other sites. Since vaginal cuff recurrence is not an uncommon site of recurrence, vaginal examination should be recommended during routine follow-up post radical cystectomy, and any abnormal vaginal secretion

or bleeding further investigated. Tumor position involving the posterior bladder, and surgery with anterior vaginectomy were statistically significant independent predictors of vaginal cuff recurrence at multivariate analysis. The anterior vaginal wall was removed to achieve negative surgical margins and to prevent local recurrence. Surprisingly, tumor stage did not predict vaginal cuff recurrence. However, anterior vaginectomy, performed in a surgical attempt to avoid local recurrence, may be seen in our study as a marker of increased risk for recurrence in the cul-de sac or in the remaining vaginal canal.

Although anterior vaginectomy is perhaps not good enough to prevent recurrence, there are no current guidelines regarding the optimal management of patients at increased risk of recurrence. These results are interesting for several reasons. First, tumor position and multifocality in the bladder must be evaluated in the preoperative setting. Adequate bladder sampling during transurethral resection and bimanual examination under anesthesia are both of great importance. A careful evaluation of preoperative imaging is also necessary before a reproductive organ sparing approach. Diffusion--weighted magnetic resonance imaging may be considered the technique of choice for local staging, as there is increasing evidence of its superior performance compared to other imaging techniques (21, 22). Second, vaginal sparing surgery should be suggested only to a select group of patients. Even if vaginal preservation has potential benefits to decrease postoperative rates of sexual dysfunction, decreased risk of pouch prolapse, and neobladder-vaginal fistula, vaginal cuff recurrence has a poor 5-year cancer-specific survival. Therefore, patient characteristics (e.g., age, performance status), patient needs (e.g., sexual desire, choice of diversion), pathological stage, and position of tumor in the bladder (organ-confined tumors away from the bladder neck, trigone, bladder base, and posterior wall) should be carefully evaluated. Any residual or recurrent disease in the pelvis is a poor predictor of overall survival and cancer-specific survival and adds to the body of literature supporting the need for meticulous extirpative surgery at the time of radical cystectomy.

The present study evaluated vaginal cuff recurrence as a specific site of relapse. This particular attention to a unique site of recurrence in the female population could explain the detection of a relatively high frequency of vaginal cuff recurrence in comparison to other published series (12, 13). Due to the well-known differences in pelvic anatomies between males and females, our results stressed the importance of gender differences in the evaluation of recurrence. Even though further studies are needed, these results add value for improved comprehension and possible prevention of bladder cancer recurrence.

However, several limitations of the study include small sample size and the small number of events which limited further statistical sub-analysis. Additionally, due to the retrospective nature of the study, certain biases may be present in the analysis. Examples include the advances in treatment and imaging technologies, different operating surgeons performing radical cystectomy, and the differences in follow-up schedules. All of these variables could not be appropriately controlled for and may have impacted outcomes.

CONCLUSIONS

Assessing the incidence and potential risk factors for development of recurrent disease among women with bladder cancer, demonstrates that vaginal cuff recurrence is associated with similar survival outcomes to recurrence occurring at other locations. The selection of appropriate candidates for a sexual-sparing procedure must carefully balance both organ preservation and oncologic control. Furthermore, careful evaluation of the location of bladder cancer prior to surgery is crucial for appropriate surgical planning. Additional studies are required to better evaluate the impact of vaginal cuff recurrence on survivorship and the appropriate management following radical cystectomy.

CONFLICT OF INTEREST

None declared.

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PCA3 rs544190G>A and prostate cancer risk in an eastern Chinese population

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ABSTRACT

Background: The association of prostate cancer antigen 3 (PCA3) polymorphism (SNP, rs544190G>A) with metastatic prostate cancer in European descent has been reported. Our aim of the current study was to re-validate the effect of PCA3 polymorphism on prostate cancer risk in an Eastern Chinese population and then estimate possible genetic discrepancies among population.

Materials and Methods: Taqman assay was employed to determine genotype of SNP rs544190 in 1015 ethnic Han Chinese patients with prostate cancer and 1032 cancer-free controls. Simultaneously, odds ratios (OR) and 95% confidence intervals (95%CI) for risk relationship were calculated by logistic regression models.

Results: The statistically significant relationship between PCA3 rs544190G>A and higher prostate cancer risk was not found. Stratification analysis revealed that there was no remarkable association of rs544190 variant AG/AA genotype with prostate cancer risk in every subgroup, except for patients with Gleason score ≤7(3+4).

Conclusion: Although the results demonstrated that SNP rs544190 was not involved in prostate cancer risk in Eastern Chinese descent, unlike in European population, these might have clinical implications on prostate cancer heterogeneity around the World. To validate these findings, well-designed studies with different ethnic populations are warranted.

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INTRODUCTION

In the Western male population, prostate cancer is the most commonly diagnosed carcinoma and the second leading cause of cancer-related deaths (1). Owing to the improvement of health care system, the change of lifestyles and the extension of life expectancy, the detection rate and thus prostate cancer morbidity in China is increasing quickly (2, 3). Prostate cancer is not easier to occur in individuals of Asian ancestry than in their white and African counterparts, and Asian descent who live in diverse environment around the World still have low risk of developing prostate cancer (4-6). Based on these evidences, some genetic factors represented individual characteristics may contribute to the diverse mechanism for prostate carcinogenesis among ethnic populations. Importantly, single nucleotide polymorphisms (SNPs) have been studied and used to track cancer-causing genes (7), and thus the analysis of SNPs may assist in the development of new mechanism and agents for treating cancer.

Long non-protein-coding RNA (lncRNA) can regulate the expression of genes in close genomic proximity and target distant transcriptional

activators or repressors via transcriptional interference, initiation of chromatin remodeling, promoter inactivation and activation of an accessory protein (8-11). Therefore, variations in lncRNAs are likely to modify functions of various biological pathways involved in prostate carcinogenesis. One of the famous lncRNA in prostate cancer is prostate cancer antigen 3 (PCA3) (12), the expression of which significantly increased in prostate tumors compared with expression in adjacent non--neoplastic prostate tissue (13). Some studies (14, 15) also revealed that the overexpression of PCA3 RNA are strongly related with malignant transformation of prostatic epithelial cells and with higher Gleason score. Therefore, further studying PCA3 polymorphism which can alter its expression and then alter its function provide clues for the clinical management of prostate cancer (13-16).

Recently, researchers (17) found that the PCA3 SNP rs544190 locates at the -845 locus of PCA3 and is a transition G>A in the promoter region, and then results in the increased expression of PCA3. Meanwhile, this SNP has been verified to be significantly associated with metastatic prostate cancer risk in European population (17). As is well-known that the results of associational studies may vary among populations due to inter-population genetic differences including differences in allele frequencies and linkage disequilibrium (LD) structures (18). Thus, it is more reasonable to re-evaluate the association of this SNP with prostate cancer risk in different cohort other than the one in which this association was identified.

In the current study, a case-control study was conducted to further validate the reported association of rs544190 with prostate cancer risk and other clinical characteristics in an Eastern Chinese cohort.

MATERIALS AND METHODS

A total of 1015 ethnic Han Chinese patients with prostate cancer from Fudan University Shanghai Cancer Center (FUSCC) between 2009 and 2012 was included in the current study. Ethnic Han Chinese is one of the ethnic groups in China and constitutes approximately 92% of the population of Mainland China. All of patients were collected from Eastern China, which includes Shanghai, Zhejiang, Jiangsu and the surrounding regions. The tissue bank of FUSCC provided samples of prostate cancer patients. Additionally, 1032 cancer-free controls of ethnic Han Chinese in Eastern China were recruited from the Taizhou Longitudinal (TZL) study with the selection criteria containing no individual history of cancer (19). Controls were frequency matched to the cases on age and sex. The present study also obtained data on environmental exposure history and demographic characteristics of each participant, such as smoking status, age, sex, ethnicity, BMI. Approximately 10 mL of blood, of which 1 mL was used for genomic DNA extraction, was collected from each participant. All of study participants have signed written informed consents. The study protocol was approved by the Institutional Review Board of FUSCC (Ethical Application Ref: 050432-4-1212B). Moreover, all methods included in protocol of this study were performed in accordance with the approved guidelines.

Genomic DNA was isolated from blood sample of participant by utilizing the QIAamp DNA blood maxi kit (Qiagen, Valencia, CA). Then, the Taqman assays (Applied Biosystems, Foster City, CA) with a 7900 HT sequence detector system (Applied Biosystems) was used to determine PCA3 rs544190G>A (Forward primer: CCAATGAACTGGGATGACACAA, Reverse primer: AGGAGAGGCAAGGAAGCTAA, probes: GTTTCATATCCCCC[G/A]TCCCCAAGAGAGGA). For the quality control, each 384-plate included four negative controls (without DNA template) and two duplicated samples. Meanwhile, the assays were repeated in 5% of the samples and 100% concordance was obtained.

For the statistical analysis conducted with SAS software (version 9.1; SAS Institute, Cary, NC), X^2 test was used to evaluate the difference in the frequency of genotype as well as demographic and other covariates between cases and controls. The good-of-fit X^2 Test was applied to estimate the Hardy–Weinberg equilibrium of genotype distributions in the controls. By utilizing regression models, crude and adjusted odds ratios (ORs) were calculated to evaluate associations between the genotypes and prostate cancer risk. The homogeneity tests were performed to explore the difference in risk estimates among subgroups. The haplotype analysis was not performed due to the selected SNP

in the same block. All tests were two-sided, and P value less than 0.05 was considered to have statistical significance.

RESULTS

As presented in our previous paper (20), significant difference in the frequency of body mass index (BMI) between cases and controls was presented (39.15% vs 24.9%, p<0.0001), except for age and smoking status. Simultaneously, the characteristics included PSA, Gleason score, TNM stage of cases were also summarized.

In the present study, the allele and genotype frequencies of SNP rs544190 in cases and controls are listed in Table-1. Taking advantage of good-of--fit X^2 Test, the researched genotype distributions for rs544190 among the controls were consistent with the Hardy-Weinberg equilibrium (p=0.119). However, no significant difference in the genotype distribution of PCA3 rs544190 between the cases and controls was observed (p=0.7291). Meanwhile, the rs544190 A allele was less frequent in controls than in cases with no significantly statistical difference (p=0.7012). In multivariate logistic regression analysis, rs544190 AG, AA and AG/AA genotypes were not correlated with significantly increased risk of prostate cancer (adjusted OR=0.988, 95%CI=0.821-1.190, p=0.8993; adjusted OR=1.123, 95%CI=0.806-1.564, p=0.494; and adjusted OR=1.011, 95%CI= 0.849-1.205, p=0.9019, respectively) when the genotype GG was used as reference and age, smoking and BMI were adjusted. Compared with the genotypes (GG/AG), there was also no significant relationship between rs544190 AA genotype and the increased prostate cancer risk in the recessive model (adjusted OR =1.128, 95%CI =0.816-1.559, p=0.4663).

Next, the correlation of the SNP rs544190 with prostate cancer risk was furtherly assessed by stratified analysis using age, BMI, smoking, Gleason score, TNM stage and aggressive status (Table-2). Nevertheless, the notable relationship between prostate cancer risk and rs544190 variant AG/AA genotypes was also not appeared in these strata. Meanwhile, there was non-significant difference in risk estimates among these strata in further heterogeneity test, except for Gleason score ≤7(3+4). The results mentioned

Table 1 - Logistic regression analysis of associations between PCA3 variant genotype and prostate cancer risk.

Variables	Genotypes	Cases no. (%)	Controls no. (%)	P [a]	Crude OR (95% CI)	Adjusted OR (95% CI) [b]	P [b]
rs544190							
	GG	573 (56.45)	584 (56.59)	0.7291	1.00	1.00	
	AG	358 (35.27)	372 (36.05)		0.981(0.815-1.181)	0.988(0.821-1.190)	0.8993
	AA	84 (8.28)	76 (7.36)		1.126(0.809-1.568)	1.123(0.806-1.564)	0.494
	AG+AA	442 (43.55)	448 (43.41)	0.9505 [d]	1.006(0.844-1.198)	1.011(0.849-1.205)	0.9019
Additive model				0.7291 [c]	1.026(0.896-1.176)	1.028(0.897-1.178)	0.6871
	GG+AG	931 (91.72)	956 (92.64)		1.00	1.00	
	AA	84 (8.28)	76 (7.36)	0.4424 [e]	1.135(0.821-1.568)	1.128(0.816-1.559)	0.4663
A allele frequency		0.2591	0.2539	0.7012			

Abbreviation: PCA3, Prostate Cancer Antigen 3; OR, odds ratio; 95% CI, 95% confidence interval; rs, reference single nucleotide polymorphism.

[a] Chi-square tests were used to calculate differences for the frequency distribution of genotypes, combined genotypes, or alleles between cases and controls; [b] Adjusted for age, smoking, and BMI status in logistic regress models; [c] For additive genetic models; [d] For dominant genetic models; e For recessive genetic models.

The results were in bold, if *P*<0.05 or 95%CI excluded 1.

Table 2 - Stratification analysis for associations between PCA3 variant and prostate cancer risk by dominant genetic model in all subjects of Eastern Chinese man.

variables	rs544190 (cases/controls)		Adjusted OR(95%CI)[a]	*P* [a]	*P* hom
	AA+AG	GG			
Age, year					
≤69 (mean)	232/242	282/287	0.976(0.746-1.247)	0.8454	0.719
>69 (mean)	210/206	291/297	1.045(0.813-1.344)	0.7315	
BMI, kg/m²					
≤25	323/271	439/357	0.970(0.783-1.201)	0.7781	0.407
>25	119/177	134/227	1.143(0.833-1.567)	0.4078	
Smoking status					
Never	183/175	223/231	1.100(0.833-1.453)	0.5019	0.496
Ever	259/273	350/353	0.957(0.763-1.199)	0.7010	
Gleason score					
≤7(3+4)	**155/448**	**162/584**	**1.254(0.974-1.615)**	**0.0793**	**0.046**
≥7(4+3)	247/448	359/584	0.898(0.732-1.101)	0.3006	
Stage of disease					
I+II	199/448	240/584	1.085(0.866-1.359)	0.4774	0.336
III+IV	207/448	291/584	0.928(0.747-1.152)	0.4979	
Aggressive [b]					
low	109/448	117/584	1.205(0.902-1.609)	0.2066	0.165
high	333/448	456/584	0.955(0.792-1.152)	0.6307	

PCA3 = Prostate Cancer Antigen 3; **rs =** reference single nucleotide polymorphism; **OR =** odds ratio; **95% CI =** 95% confidence interval; **P hom =** Homogeneity test; **BMI =** body mass index.

[a] Obtained in logistic dominant models with adjustment for age, smoking status and BMI; [b] Lowly aggressive status refers to Gleason score <7 or PSA ≤10ng/mL or cT stage <cT2b; Highly aggressive status refers to Gleason score ≥7 or PSA >10ng/mL or cT stage ≥cT2b.

The results were in bold, if $P<0.05$.

above indicated that there might exist potential correlation of PCA3 rs544190 with Gleason score.

DISCUSSION

The association of prostate cancer risk with PCA3 polymorphism -845G>A was mainly determined in the present study, and also was firstly evaluated in an Eastern Chinese population.

Increasing evidences (21-23) have shown that lncRNAs are involved in transcription, splicing, translation, protein localization, cellular structure integrity, imprinting, cell cycle and apoptosis, stem cell pluripotency and reprogramming and heat shock response. Furthermore, researchers have found that lncRNAs play a very vital role in pathological conditions such as cancer and cardiovascular disease and consequently provide

novel biomarkers and pharmaceutical targets (24, 25). To the best of our knowledge, polymorphisms which are responsible for change in gene expression or function can be characterized as functional genetic variants (26). These evidences mentioned above have indicated that variation in lncRNA regions may contribute to the etiology of disease.

In the current study, the rs544190 AA genotype of PCA3, as one of lncRNAs, was not detected to be correlated with increased prostate cancer risk. Meanwhile, there was also non-significant association of genotype AG and AG/AA with the higher risk of prostate cancer. However, a previous study showed that A allele carriers possess an increased risk for developing metastatic prostate cancer (17). Differences in research participants, sample size and ancestral background might lead to inconsistent results among various studies. To further research the relationship between previously reported risk loci and prostate cancer risk instead of metastatic prostate cancer risk, the present study with the larger number of subjects was timely designed and conducted.

By stratified analysis using age, BMI, smoking, Gleason score, TNM stage and aggressive status, the statistically significant association of PCA3 rs544190 with increased prostate cancer risk in every subgroup was not found. Other studies (13, 17) have also indicated no significant relationship between allele and elevated Gleason score in prostate cancer. Such findings mentioned above might be interpreted by the fact that there was still not enough number of participants to provide statistical power to detect any relationship in stratified analysis. Additionally, cancer is a complex and multifactorial disease so that a single genetic variant is insufficient to predict the overall risk. Therefore, larger number of participants and more SNPs in lncRNAs or in other related gene related with the etiology of prostate cancer should be considered in the future studies.

Here, limitations in the current study need to be addressed. Firstly, bias from selection of the non-representative population would not be absolutely excluded because it was a hospital-based case-control study with patients from FUSCC and controls from TZL study (19). By means of frequency-matching cases and controls on age, areas of residence and further adjustment for possible confounding factors in final analysis, potential confounding bias might be furthest minimized. Secondly, owing to the nature of retrospective study design, reliable and sufficient information about exposure data were not available. Finally, genetic variations discovered through association studies are rarely the actual causal variant-rather, they may/mayn't be associated with disease risk for linkage disequilibrium which sometimes extends over relatively large distances in the human genome (27). Thus, an integrated and systematic approach needs to explore the mechanisms that increase the risk for cancer. In the future, these limitations would be conquered via larger, well designed and prospective population-based studies.

CONCLUSIONS

Although the current study has found that the polymorphism PCA3 -845 G>A was not correlated with progression to prostate cancer in an Eastern Chinese population, this might have clinical implications on prostate cancer heterogeneity around the World. Larger and more in-depth molecular studies for exploring the role of rs544190G>A in prostate cancer are warranted before it may be contributed to clinical decision-making.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Nephrogenic adenoma of the bladder: a single institution experience assessing clinical factors

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ABSTRACT

Introduction: Nephrogenic adenoma (NA) was first described by Davis in 1949 as a "hamartoma" of the bladder. There are many proposed predisposing factors for NA including chronic inflammation, renal transplantation, and bladder cancer. We examined our experience with NA to determine predisposing factors and determine if there was any increased risk for development of subsequent malignancy.

Materials and Methods: All patients with a pathologic diagnosis of bladder NA from 2001-2013 were included. Patient history, clinical factors including possible predisposing factors for NA, and follow-up were reviewed.

Results: Among 60 patients, 68% were males with an average age of 61, an average BMI of 28.7, and 60% had a smoking history. In evaluating pro-inflammatory factors, 26.7% underwent either Bacillus Calmette-Guerin or mitomycin C, 30% had recurrent urinary tract infections, and 25% had a history of catheterization. Recurrence of NA after initial resection occurred only in 14.7% of patients who underwent follow-up cystoscopy. A history of concurrent bladder cancer was seen in 41.7% of patients, but there were no cases of *de novo* bladder cancer diagnosed after NA.

Conclusion: To the best of our knowledge, this is the largest series of patients with NA of the bladder. NA occurs in a heterogeneous population of patients, but most often with underlying inflammation. NA occurred concurrent with bladder cancer; however there were no cases of *de novo* bladder cancer after NA, reassuring that NA is likely a benign reactive condition.

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INTRODUCTION

Nephrogenic adenoma (also called nephrogenic metaplasia) was first described in 1949 as a hamartoma of the bladder – a "tumor-like nodule of superfluous tissue retaining the basic structure of the tissue in which it was situated and differentiated from it by hyperplasia" (1). In 1950, the term 'nephrogenic adenoma' (NA) was coined in a case series of patients describing similar pathologic findings in the bladder (2). Small case series have reported NA occurring concurrently with bladder cancer (3, 4-7). Though TCC may be concurrent with the findings of nephrogenic adenoma, malignant transformation of nephrogenic adenoma has only been demonstrated in a few small case series (8-10). The predisposing factors for this lesion are poorly understood, though many studies will report prior trauma or inflammation to play a role in the development of NA such as recurrent urinary tract infections, chronic catheterization or administration of intravesical therapy (3-5, 7, 8, 10-15). Given its rarity, there are very few large series to assess these concerns and no clear guidance on its management and follow-up (16).

We examined our institution's experience with patients diagnosed with nephrogenic adenoma of the bladder to determine any predisposing factors for nephrogenic adenoma and also to determine if any patients subsequently developed a *de novo* bladder cancer.

MATERIALS AND METHODS

This study was approved by our Institutional Review Board. Utilizing our institution's pathology database, we compiled all patients diagnosed with NA of the bladder from 2001-2013. Only patients with an initial, *de novo* diagnosis were included. NA of the upper tract or other locations other than the bladder was not included in this retrospective review. The pathology slides and compilation of pathology reports were completed by the genitourinary pathologists at our institution.

Possible predisposing factors as well as other clinical history were reviewed. These included prior catheterizations, urologic history, recurrent infections, history of transplant, and concomitant bladder cancer. Concurrent bladder cancer diagnosis was defined as a patient with nephrogenic adenoma and bladder cancer in the same specimen. We also tracked any patients with a *de novo* diagnosis of bladder cancer subsequent to their diagnosis of NA. Recurrence of NA was defined as a patient completely treated for NA with resection that subsequently developed a new lesion.

RESULTS

Sixty patients with NA of the bladder were identified. The average age at diagnosis was 61 (range 8-91). There was only one pediatric patient. The majority of the population was male (68.3%) and had a smoking history (58.3%). There were only 3 (5%) patients with a history of renal transplant and 21 (35%) patients with a history of chronic kidney disease. All but two patients had prior urologic history including prostate cancer, interstitial cystitis, bladder cancer and neurogenic bladder (Table-1). Fifteen (25%) patients were found to have been intermittently catheterized or have a current indwelling Foley catheter and 18 (30%) patients had a prior history of recurrent urinary tract infections defined as greater than or equal to three infections in a year. The most common presenting symptoms were lower urinary tract symptoms (35%) and hematuria (28.3%) (Table-2).

The surgical specimens on which NA were diagnosed included 14 transurethral resections (TURs), 34 biopsies, and 10 cystectomies for concurrent advanced bladder. Previous bladder cancer history was present in 25 (41.7%) patients and 16

Table 1 - Patient Characteristics.

Gender	
Male	68% (n=41)
Female	32% (n=19)
Average BMI	28.7
Average age at diagnosis	61 years (range 8-91)
Smoking history	58% (n=35)
History of Bladder Cancer	41.7% (n=25)
Trauma/Irritative Risk Factors	
History of Intravesical Therapy	26.7% (n=16)
History of CIC/Catheter	26.7% (n=16)
History of recurrent UTI	30% (n=18)

BMI = body mass index; **CIC =** clean intermittent catheterization; **UTI =** urinary tract infection

Table 2 - Presenting Symptoms Prior to Cystoscopy.

Symptoms	Number of Patients
LUTS	21 (35%)
Hematuria	15 (25%)
Asymptomatic	9 (15%)
Incontinence	8 (13%)
Dysuria	4 (7%)
Recurrent UTI	4 (7%)
Urinary Retention	4 (7%)
Flank Pain	2 (3%)
Stone	1 (2%)
Other	1 (2%)

LUTS = lower urinary tract symptoms; **UTI =** urinary tract infection

(26.7%) had undergone Bacillus Calmette-Guerin or mitomycin C instillations. Ten of the patients had NA diagnosed concurrently with their bladder cancer. Ten of the patients had NA diagnosed only on the cystectomy specimen with no prior NA diagnosis. Two other patients had cystectomies for invasive bladder cancer following their diagnosis of NA and known concurrent bladder cancer.

Of the 50 patients who had not undergone cystectomy, thirty-four patients had a follow-up cystoscopy. Recurrence was noted in 5 (14.7%) patients. Three of the patients had diffuse involvement of the bladder with NA at presentation and were likely incompletely resected while two of them had only singular small areas of NA. All were managed with biopsy and/or resection along with fulguration. In the setting of diffuse involvement of the bladder (more than 25% of the bladder surface involved) these often required multiple fulgurations for relief of symptoms and clearance of the lesions. None of these patients with recurrence had a history of bladder cancer or concurrent bladder cancer. Overall, despite the high proportion of patients with bladder cancer in this series, no patients were diagnosed with a bladder cancer after NA at an average follow-up of 10.1 months.

DISCUSSION

NA is still considered a rare finding; however, reports of its occurrence have increased since its initial description in 1949 (Table-3). Direct cystoscopic visual findings of these lesions (Figure-1) are varied across multiple studies but often can mimic other urologic conditions such as urothelial carcinoma or chronic cystitis (16). There too exists variation in subtypes of the NA pathologic findings. Figure-2 shows an example of a pathology slide at 200 magnification showing papillary cores that are lined by a single layer of cuboidal epithelium which contain acinar structures and dilated tubules. To our knowledge, this is the largest clinical cohort of NA of the bladder published. This study found that the most common presentation of NA is lower urinary tract symptoms and hematuria, which according to AUA Guidelines would lead to an evaluation with a cystoscopy (17). Other presentations included retention, dysuria, recurrent UTIs and some were asymptomatic. The exact etiology of nephrogenic adenoma has not been identified, but there are reports of patients with renal transplantation being at risk for developing nephrogenic adenoma (3, 6). Mazal et al. looked at NA in patients with kidney transplantation and found that the cells originated from the donor kidney tubular cells and not from the urothelial mucosa. It is likely that seeding from the kidney of these renal-like cells is the same etiology in non-transplant patients (8).

Similar to the majority of other studies, we found a male predominance (2, 5, 7, 11, 12). Though this study focused on NA of the bladder, other studies have assessed other locations but all showed bladder as the most common location (4, 5, 11, 12). Similar to prior studies most of our patients had well-defined urologic issues prior to the diagnosis, including recurrent urinary tract infections, benign prostatic hyperplasia, interstitial cystitis or urothelial cell carcinoma (3-5, 7, 8, 13-15).

The vast majority of studies have supported that NA is a benign lesion (3-5, 7, 11); NA is not associated with deep invasion, mitotic activity, neoplastic-type atypia, or de-differentiation. NA generally grows slowly, and there has been no convincing evidence of any malignant transformation of NA (1, 2, 4, 11, 12).

Though multiple studies demonstrate the benign pathologic findings along with clinical absence of progression to malignancy (2, 4, 5, 11, 12, 18), a single study reported a case of nephrogenic adenoma that ultimately developed into adenocarcinoma 2 years later with later findings of metastatic adenocarcinoma. They refer to studies in which the association between nephrogenic metaplasia and clear cell adenocarcinoma was seen in the Pax 8 staining seen in both but not with urothelium, prostatic adenocarcinoma or urothelial carcinoma. This case study, however, may instead represent what has been described as a clear cell adenocarcinoma with diffuse areas mimicking NA (8). Other studies have also reported the possible relation between nephrogenic adenoma and mesonephric adenocarcinoma warranting aggressive follow-up and management, but these

Table 3 - Summary of publications reviewing patients with nephrogenic adenoma of the bladder.

Authors	Publication Year	Study Population	Association with Bladder Cancer	Presenting Symptoms	Risk Factors	Recurrence	Conclusion
Kaswick et al. (13)	1976	2	No	Hematuria Incontinence	History of prior urosurgery History of UTI	1 recurrence	-treatment with TUR, antibiotics -monitor for recurrence
Molland et al. (15)	1976	3 patients	No	Unknown	Unknown	Unknown	Malignant transformation to adenocarcinoma in one patient
Ford et al. (4)	1985	70 (35 within bladder)	7 patients with TCC	Incidental findings	History of prior urosurgery	15 patients	No malignancy in 12 year follow up
Oliva et al. (5)	1995	80 (42 within bladder)	No	N/A	Prior urosurgery nephrolithiasis infection	N/A	NA with bland cytologic features
Peeker et al. (6)	1997	31 (24 within bladder)	7 patients with UCC	Hematuria Urinary frequency Bladder Pain	History of renal transplant (1) History of prior urosurgery History of UTI	7 patients	-Trauma to urothelial mucosa may lead to NA - TUR as method of management
Tse et al. (18)	1997	22	6 patients with TCC	Hematuria Urinary frequency Incidental	History of renal transplant (7) Recurrent UTI History of prior urosurgery	6 patients	With association to TCC, NA should be taken seriously and followed up
Porcaro et al. (12)	2001	8	3 patients with TCC	Hematuria Irritative voiding symptoms	History of prior urosurgery	5 patients	-Features of NA nonspecific but TUR will diagnose & treat -high recurrence rate requiring follow up
Chen et al. (11)	2006	8	No	Hematuria Urinary frequency	History of urosurgery History of catheterization History of UTI	3 patients (median relapse 7 months)	-NA is a benign lesion -recurrence is high
Hungerhuber et al. (19)	2008	1	Progression to adenocarcinoma	Hematuria	History of urosurgery	Yes	NA may have malignant potential and warrants follow up
Dhaliwal et al. (10)	2012	1	Progression to Clear cell adenocarcinoma	Hematuria Proteinuria	History of urosurgery	No	Malignant transformation can occur with NA
Kuzaka et al. (3)	2014	3	1 patient with TCC	Hematuria	History of recurrent UTI History of prior urosurgery	2 patients (5 and 9 months)	-NA is a benign lesion -Recurrence is high
Gordetsky et al. (7)	2016	31 (26 within bladder)	12 patients with UCC	Hematuria Urinary incontinence Hydronephrosis Asymptomatic	History of renal transplant (1) History of DM (8 patients)	1 patient	-NA is a benign lesion

TCC = transitional cell carcinoma; **N/A =** not applicable; **NA =** nephrogenic adenoma; **UCC =** urothelial cell carcinoma; **TUR =** transurethral resection; **DM =** diabetes mellitus

Figure 1 - Cystoscopic findings of nephrogenic adenoma mimicking other urology pathology.

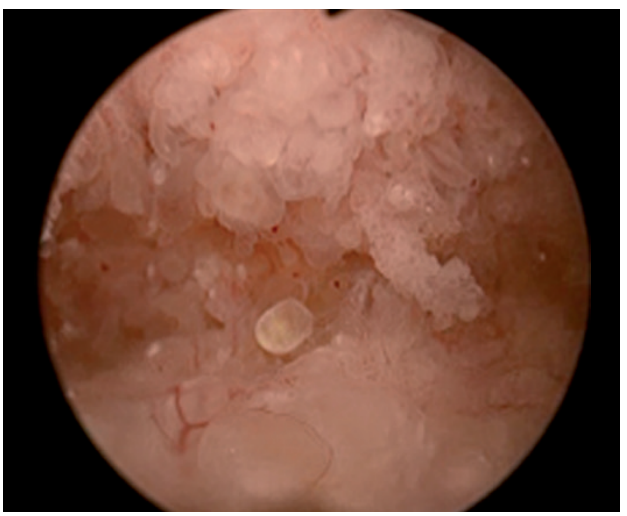
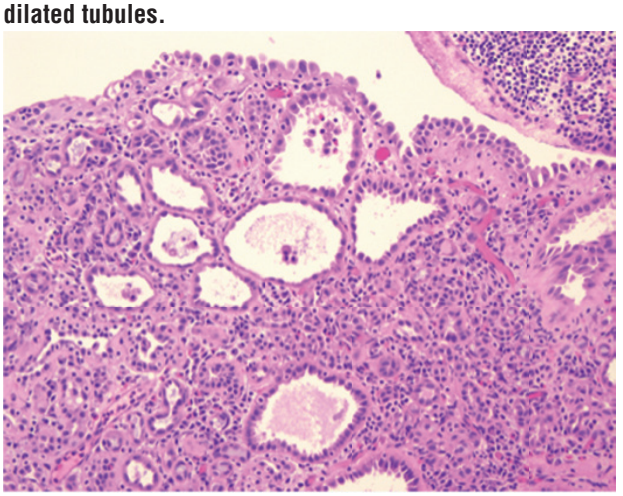


Figure 2 - The papillary cores are lined by a single layer of cuboidal epithelium. They contain acing structures and dilated tubules.



studies are rather old (9, 19). Overall, the vast majority of the recent literature, including our study, supports that NA is a benign reactive lesion with no associated increased risk of the development of bladder cancer.

There are no guidelines at present on the management and follow-up of nephrogenic adenoma. Recurrence rates have differed across studies. Our study showed recurrence in five patients and Gordetsky's recent study found one in 31 patients with recurrence. Other studies had varying numbers of recurrence, but recommendations were made to have long term follow-up as recurrences were common (5-8, 13, 14, 20). Given the symptomatic nature of this lesion and its tendency to recur, it would be prudent to follow patients with a cystoscopy and treat any of these recurrences. The exact timeline of cystoscopic follow-up is unknown, but based on the studies reviewed, patients were already on a surveillance schedule based on their history of bladder cancer and/or they presented with recurrent symptoms of hematuria or lower urinary tract symptoms which would prompt a re-evaluation. Follow-up noted in each of the studies varied largely from 2-24 months with reported average recurrence occurring within the first year (3, 13). We would recommend standard follow-up for bladder cancer patients. A possible plan for patients with nephrogenic adenoma alone may be a follow-up cystoscopy within 6-12 months from the initial diagnosis and then with symptom recurrence. Larger studies with longer follow-up will best answer this question.

Based on our review, this is the largest study of a cohort of 60 patients with an average 10.1 month follow up of patients with nephrogenic adenoma of the bladder. However, we do recognize there are limitations to the conclusions from this study. This is a retrospective chart review of patients identified by our pathology database. Our average follow-up was only 10.1 months, and only 68% of the population with intact bladders underwent follow-up cystoscopy. There is also likely a selection bias favoring more severe disease involvement as likely only symptomatic patients and/or patients with a history of bladder cancer would undergo cystoscopy and there are likely asymptomatic patients in the community who have small non-symptomatic lesions that we do not capture.

CONCLUSIONS

In conclusion, patients with nephrogenic adenoma represent a heterogeneous population with varying presentations that cover the wide span of urologic subspecialties. NA has not been shown to lead to malignant progression in this study and in the majority of the literature. There is a predilection for patients that are male with prior

urologic conditions; the most common presenting symptoms being lower urinary tract symptoms or hematuria. Recurrence does occur, but was noted to be relatively uncommon in this study. As for management, patients who are under surveillance for bladder cancer should continue the surveillance schedule with biopsy/resection of lesions that may appear suspicious as per usual regimen. Patients with a diagnosis of only nephrogenic adenoma should likely undergo repeat cystoscopy to confirm eradication of the lesions after resection, but given the limited data a follow-up regimen is difficult to establish.

CONFLICT OF INTEREST

None declared.

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Differences in the percutaneous nephrolithotomy practice patterns among Latin American urologists with and without endourology training

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ABSTRACT

Purpose: Although the worldwide percutaneous nephrolithotomy (PCNL) practice patterns determined via a survey sent to members of the Endourological Society have been published, differences in PCNL practice patterns among Latin American urologists based on endourological or lithiasis training have not been published.

To determine the PCNL practice patterns among Latin American urologists with and without training in endourology.

Materials and Methods: The SurveyMonkey® web platform was used to develop a 27-item survey on PCNL for the treatment of renal stones, and the survey was sent via e-mail and other electronic media to 2000 urologists from 15 Latin American countries. Endourology-trained (group 1) and nontrained urologists (group 2) were analyzed. The group results were compared using the chi-squared and Fisher's exact tests. SPSS version 20 for Windows was used for all analyses.

Results: A total of 331 urologists responded to the survey (rate of 16.55%): 221 (66.7%) in group 1 and 110 (33.2%) in group 2). In groups 1 and 2, 91.9% and 63.2% performed PCNL, respectively; 85.1% and 58.5% used preoperative tomography, respectively; 12.7% and 4.7% used preoperative nephrolitometry nomograms, respectively; 45.2% and 32.1% used endoscopic combined intrarenal surgery, respectively; 68.3% and 38.7% used multiple percutaneous tract realization, respectively; and 19.9% and 5.7% used minimally invasive PCNL, respectively (all p=0.0005).

Conclusions: Statistically significant differences were observed in PCNL practice patterns of Latin American urologists with and without training in endourology. Specific training in endourology significantly influence the practice patterns of Latin American urologists.

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INTRODUCTION

Currently, percutaneous nephrolithotomy (PCNL) is the gold standard treatment for renal stones >20mm and >15mm in diameter that are located in an inferior renal calyx (1, 2). In recent years, PCNL procedures have significantly increased worldwide. Although PCNL is an established procedure with specific indications, differences are observed in the practice patterns among urologists worldwide (3), which has contributed to significant differences in surgical procedures, preoperative planning, and postoperative management. These significant differences could impact the final surgical outcomes and may occur because of factors that

include the urologist's training, experience and case volume and the practice setting. Because PCNL is a multiple step procedure, the likelihood of modifications by urologists at every single step is increased.

Until recently, few reports have been published on the particular practice patterns among urologists, and these studies were mainly conducted in the United States and Europe (3-5). Moreover, limited data are available on the practice patterns among Latin American urologists. Therefore, our aim was to evaluate the practice patterns among Latin American urologists and compare the impact of endourology training on the performance of PCNL. Endourology training is defined as a post-residency sub-specialization in all minimally invasive surgeries, including percutaneous surgery for urinary stones treatment. To our knowledge, this study is the first to report information on the PCNL practice patterns of urologists in relation to endourology training.

MATERIALS AND METHODS

The web platform SurveyMonkey® was used to create a 27-item anonymous survey on the PCNL for renal stone treatment (see appendix). The survey was sent via e-mail and other electronic media to 2000 urologists from 15 different Latin American countries, and a Whatsapp group was created for communication among the main urologists in each country. The survey collected information on the demographics, age, nature of the practice, training in endourology (defined as a post-residency sub-specialization specific for urinary stones treatment) and preoperative, perioperative and postoperative variables. The results were analyzed based on the following two groups: endourology-trained urologists (group 1) and nontrained urologists (group 2) that reported to do PCNL and we excluded from the comparative analysis those urologists that do not perform PCNL. The group results were compared using the chi-squared test and Fisher's exact test. The statistical program SPSS version 20 for Windows was used for all analyses. Statistical significance was defined at a p-value <0.05.

RESULTS

Demographic data

A total of 331 participants from 15 different countries responded to the survey (rate of 16.55%) Table-1. Of these, 257 of participants (77%) were under 50 years old and 74 >50 years old (23%). A total of 173 of the 257 participants under 50 years old (67.3%) reported having endourological training, whereas 48 (64.9%) of the 74 participants >50 years old reported endourolo-gical training, with no statistically significant difference between age group among trained and not trained urologists (p-value 0.403). Of the total number of participants, 221 (66.7%) respondents had endourology training, and 110 (33.2%) participants did not have endourology training.

Table 1 - Participants by country.

Country	N	Percentage
Mexico	84	25.4%
Argentina	48	14.5%
Brazil	35	10.6%
Colombia	20	6%
Uruguay	18	5.4%
Peru	16	4.8%
Dominican Republic	11	3.3%
Ecuador	4	1.2%
Paraguay	15	4.5%
Venezuela	34	10.3%
Chile	12	3.6%
Nicaragua	15	4.5%
El Salvador	1	0.3%
Guatemala	9	2.7%
Panama	9	2.7%

For the subsequent analysis we excluded those urologists who do not perform PCNL and we created two groups for comparing those trained and not trained, as stated in our methods. In groups 1 and 2, 91.9% and 63.2% of participants performed PCNL (p=0.0005). Thus, the trained

urologists performed significantly more PCNL procedures per year than the nontrained urologists (p=0.0005) (Table-2).

Preoperative considerations

With respect to the preoperative considerations, 72.9% and 51.9% of the urologists in groups 1 and 2 used renal stones >20mm as an indication for PCNL (p=0.0005), respectively; 27.1% and 11.3% of the urologists in groups 1 and 2 used renal stones >15mm in the lower pole calyx as an indicator for PCNL (p=0.003), respectively; 85.1% and 58.5% of the urologists in groups 1 and 2 considered preoperative tomography necessary (p=0.0005), respectively; and 12.7% and 4.7% of the urologists in groups 1 and 2 used preoperative nephrolithometry scores as an indicator (p=0.0005).

Table 2 - Case volume per year for the trained and nontrained urologists.

Case volume/ year	Trained urologists	Untrained urologists	p-value*
1-10	59 (26.7%)	27 (25.5%)	
11-30	63 (28.5%)	24 (22.6%)	
31-60	41 (18.6%)	10 (9.4%)	0.0005
61-100	23 (10.4%)	4 (3.8%)	
>100	15 (6.8%)	1 (0.9%)	

*Fisher's exact test was used. Differences were statistically significant at p-values <0.05.

Perioperative variables

Of the urologists with and without endourology training, a total of 45.2% and 32.1% used the practice pattern of endoscopic combined intrarenal surgery (ECIRS) (p=0.0005), respectively; 68.3% and 38.7% used multiple percutaneous tract realization of each group (p=0.0005), respectively; and 19.9% and 5.7% used minimally invasive percutaneous nephrolithotomy (MiniPERC) (p=0.0005), respectively (Table-3). Only 7 participants (2.1%) of the total reported performing percutaneous puncture guided by ultrasound.

Postoperative conduct

At the end of the procedure, the nephrostomy tube was left in place more frequently by the untrained urologists than by the endourology-trained urologists, and the difference was statistically significant (p=0.0023). Tomography was more frequently used as the stone-free evaluation method by untrained urologists (Table-3).

DISCUSSION

PCNL is a complex minimally invasive procedure for renal stone treatment, and reports have shown that the outcomes are dependent on the case volume and experience of the surgeons. Kadlec showed that the in-hospital mortality rates were lower at higher-volume centers (6), and Withington demonstrated that the length of the hospital stay was shorter in higher-volume units (7, 8). These results may be related to the different practice patterns of urologists dedicated predominantly to stone disease and urologists who are more generalized. Moreover, practice patterns vary among urologists worldwide (5). Our study showed that significant differences occurred in the PCNL practice patterns between trained and untrained urologists in Latin America.

In a survey completed by Endourological Society members, 62% of respondents reported that they had received endourology training (5). Latin American urologists have a similar percentage of endourology training, with 66.7% of our respondents reporting that they had received endourology training.

As mentioned above, one of the most important influencing factors on surgical outcomes is a surgeon's case volume, and our results showed that Latin American urologists with training in endourology performed a significantly larger number of PCNL procedures than urologists without training. Thus, a proportional relationship was observed, with improved surgical outcomes observed for urologists with a greater case volume of PCNL procedures per year.

The American Urological Association and the European Urological Association have established that PCNL is the gold standard for the treatment of renal stones >2cm because the PCNL procedure has a better stone-free rate than other minimally invasive treatments. However, recent im-

Table 3 - Comparison of variables between urologists with and without endourology training.

Fluoroscopic puncture technique	Trained	Untrained	p-value*
Bull's eyes	59 (29.5%)	19 (28.3%)	
0-90 degrees	67 (33%)	14 (20.9%)	0.01
Triangulation technique	64 (31.5%)	31 (46.2%)	
Other	13 (6.4%)	3 (4.5%)	
Preferred position			
Prone	124 (61.1%)	48 (71.7%)	
Supine (Valdivia)	19 (8.6%)	5 (7.5%)	0.01
Supine (Valdivia-Galdakao)	50 (24.6%)	11 (16.4%)	
Other	10 (4.9%)	3 (4.5%)	
Dilation method			
Amplatz	74 (33.5%)	67 (63.2%)	0.005
Alken	108 (48.9%)	24 (22.6%)	0.0001
Baloom	13 (5.9%)	5 (4.7%)	0.6654
One shot	16 (7.2%)	8 (7.5%)	0.9205
Other	10 (4.5%)	2 (1.9%)	0.2350
Preferred method for postopera-tive stone status			
Tomography	123 (55.7%)	79 (74.5%)	0.0010
USG	14 (6.3%)	2 (1.9%)	0.0809
Radiography	36 (16.3%)	15 (14.2%)	0.6178
Radiography & USG	37 (16.7%)	10 (9.4%)	0.0779
Other	11 (5%)	0 (0%)	0.0195
Catheters after procedure			
Nephrostomy only	138 (62.4%)	84 (79.2%)	0.0023
Nephrostomy & catheter	60 (27.11%)	20 (18.9%)	0.130
Catheter only	7 (3.2%)	0 (0%)	0.0640
Complete tubeless	6 (2.7%)	0 (0%)	0.0869
Other	10 (4.5%)	2 (1.9%)	0.2350

*Fisher's exact test was used. Differences were statistically significant at p-values <0.05.

provements in flexible ureteroscopes have led to the preference of flexible ureteroscopy for the treatment of renal stones of 2-3cm among a number of urologists at high-volume centers (9, 10).

In a study from the United Kingdom, 29% of the PCNL procedures were performed for renal stones >2cm; 33% of the PCNL procedures were performed for renal stones at 1-2cm; and 9% of the PCNL procedures were for stones <1cm (11). These findings show that a greater percentage of PCNL procedures in the United Kingdom corresponded to stones with diameters from 1-2cm. However, our data showed that a greater number of Latin American urologists with training in endourology preferred performing PCNL for renal stones >2cm compared with non-trained urologists (72.9% vs. 51.9%) (Table-4).

Computed tomography (CT) is the cornerstone for PCNL surgical planning, and AUA

guidelines state that CT should be performed for all patients prior to PCNL. Our study showed that CT is more frequently performed before surgery by urologists with endourological training than by urologists without training, and the differences were statistically significant. This pattern could indicate that trained urologists perform more careful surgical planning than those without training, which could represent an additional factor that could influence the final surgical outcomes.

Regarding surgical planning and patient counseling, previous studies have not evaluated ogists were less likely to perform miniperc procedures than trained urologists (5.7% vs. 19.9%, p=0.0005). The purpose of this study was not to investigate the preference of other treatment options for stones <20mm among urologists, such as extracorporeal shock wave lithotripsy, fURS, miniperc, ultraminiperc and microperc. In this study, we investigated only the miniperc preferences for renal stones among the surveyed urologists; therefore, further investigations are required to determine the preferences of urologists for the endourological treatments for stones <20mm.

Table 4 - PCNL by indicator among urologists with and without endourology training.

Indication	Endourology training	Without endourology training	p-value*
Renal calculi >20mm at any location	161 (72.9%)	55 (51.9%)	0.0005
Calculi >15mm at any location	60 (27.1%)	12 (11.3%)	0.003
Calculi <20mm in lower pole calyx	77 (34.8%)	24 (22.6%)	0.033
Multiple renal calculi	106 (40%)	31 (29.2%)	0.001
Horseshoe kidney	74 (33.5%)	28 (23.6%)	0.043

*Fisher's exact test was used. Differences were statistically significant at p-values <0.05.

the rate at which nephrolithometry scores are used by urologists. These scores are useful for predicting stone-free and transfusion rates as well as the likelihood of complications after PCNL (12-15). However, although the use of nephrolithometry scores is not common among Latin American urologists, urologists with endourological training use these scores significantly more often than urologists without training (12.7 vs. 4.7%).

Trauma to renal parenchyma and bleeding are associated with the tract size. To minimize tract-associated morbidity in PCNL, various urologists worldwide have applied the minimally invasive PCNL procedure (miniperc) followed by the micro-PCNL (microperc) and the ultramini PCNL (UMP) procedures (16-18).

Miniperc defined as a percutaneous tract diameter between 15-20Fr (19) has been used to treat medium-sized (10-20mm) renal stones in 11.7% of patients in high-volume centers (20); thus, it has become popular among urologists. Our data showed that nontrained Latin American urol-

ECIRS was developed to minimize multiple percutaneous tracts (21); however, our results showed that the percentage of ECIRS procedures and the number of multiple percutaneous tracts was higher in trained urologists than in those who were not trained. A possible explanation for this finding could be that trained urologists performed more PCNL procedures annually than untrained urologists; thus, trained urologists treat more complex cases. Another explanation for this finding could be related to the greater experience and self-confidence of high-volume surgeons.

Tubeless and totally tubeless drainage options are recent modifications of PCNL, and a recent meta-analysis showed that tubeless PCNL has potential advantages, including reduced postoperative pain and analgesia requirements, shorter hospitalizations and convalescence periods, and lower costs (22). However, Sivalingam and coworkers reported that 76% of urologists (participants were members of the Endourological Society) continued to place a nephrostomy tube at the

end of the procedure (5), and Armitage reported that 53% of urologists in the United Kingdom continued to place a nephrostomy tube at the end of the PCNL procedure.

Thus, it appears that urologists worldwide favor the placement of a nephostomy tube for postoperative drainage, which continues to be the predominant procedure upon completion of PCNL. In Latin America, our results showed that nephrostomy tube drainage was the most common postoperative practice pattern; however, our comparison of trained and untrained urologists showed that nephrostomy tube co-location was significantly reduced and ureteral catheter placement (tubeless) was preferred by the trained urologists (Table-3).

The totally tubeless drainage option has a low acceptance rate among urologists, and Armitage reported that only 14% of urologists in the United Kingdom do not place a tube after the procedure (including a ureteral catheter) (11). In contrast, totally tubeless drainage (no nephrostomy and no ureteral catheter) has a high preference rate by trained urologists in Latin America; however, significant differences were not observed in the preference rate compared with untrained urologists (Table-3).

CT represents the gold standard imaging procedure for the detection of upper urinary tract stones, and the sensitivity and specificity have been reported to exceed 95% and 99%, respectively. Thus, CT is the ideal scan for evaluating the stone-free rate at the end of any endourological procedure for urinary stone treatment, including PCNL (23).

Sountoulides and colleagues observed that routine follow-up with unenhanced CT is beneficial for patients and complete eradication of stones is essential because of a higher risk of recurrent stone formation (23). However, trained urologists in Latin America show a reduced preference for the use of CT for stone-free rate evaluations.

Determining how training in endourology could affect the practice patterns among urologists dedicated to stone treatment is important, and such training could explain the difference in final surgical outcomes and perioperative and postoperative complications. Our results clearly show that the practice patterns between trained and nontrained urologists differ; however, follow-up studies are necessary to determine the factors that could explain the differences in these practice patterns.

Because our data were obtained via an electronic survey completed by urologists, the findings cannot be used to reflect the exact practice patterns of urologists or establish precise explanations of the observed trends (like the equipment and the access to new technology that each urologist could have); however, the results have some merit. Although our response rate was low (16.55%), it is similar to previous studies reporting a response rate of 14-20% (5, 24-25).

A strength of our study is that it is the first to evaluate the practice patterns of PCNL among urologists in Latin America with and without endourology training.

CONCLUSIONS

Significant differences were observed in the PCNL practice patterns between Latin American urologists with and without endourology training. The preoperative use of nephrolitometric scales and tomography, minimally invasive PCNL, and combined management (ECIRS) and a greater percentage of multiple percutaneous tracts are more commonly observed with trained urologists. Finally, trained urologists have a greater case volume per year than nontrained urologists. Endourology training appears to influence the practice patterns of Latin American urologists when performing PCNL procedures and should be encouraged.

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CONFLICT OF INTEREST

None declared.

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Appendix

Survey: Percutaneous Nephrolithotomy in Latin America

1. What is your age?

<30
30-40
41-50
51-60
>60

2. In which country is your current urology practice?

3. In what state or province do you currently work?

4. Do you have any training or a fellowship in endourology/percutaneous renal surgery or lithiasis?

Yes
No

5. Do you perform percutaneous renal surgery for the treatment of kidney stones?

Yes
No

6. How many percutaneous nephrolithotomies do you perform per year?

1-10
11-30
31-60
61-100
>100

7. Is percutaneous renal surgery your preferred treatment for certain types of renal lithiasis?

Yes
No

8. In what specific cases do you consider percutaneous renal surgery as the first-line treatment choice for kidney stones? Indicate all cases.

Calculus greater than 20 mm in any renal localization
Calculus greater than 15 mm in any renal localization
Calculus less than 20 mm in the lower calyx
Multiple renal stones
Calculus in horseshoe kidney
Other (please specify)

9. Do you routinely perform a computerized tomography scan of your patients to plan the surgery?

Yes
No

10. Do you use any pre-surgical nomograms or scores to predict the free-lithium status?

Yes (specify which)
No

11. Which of the following do you most commonly use to perform percutaneous puncture in the treatment of kidney stones?

Ultrasound
Fluoroscopy
Tomography
Other (please specify)

12. In fluoroscopic puncture, what technique do you use?

Eye of the needle
0-90 degrees
0-30 degrees
Other (please specify)

13. What is the average time of fluoroscopy application during percutaneous nephrolithotomy?

14. If necessary, do you perform more than one percutaneous tract in the treatment of renal stones?

Yes

No

15. In what position do you prefer to place the patient to perform percutaneous nephrolithotomy for renal stone treatment?

Prone

Supine (Valdivia)

Supine (Valdivia - Galdakao)

Other (please specify)

16. Do you perform endoscopic combined intrarenal (ureteroscopy+nephrostomy) retrograde surgery for renal stone management?

Yes

No

17. In what position do you perform endoscopic combined intrarenal surgery (ureteroscopy+percutaneous nephrolithotomy)?

Prone

Supine (Valdivia)

Supine (Valdivia - Galdakao)

Other (please specify)

18. What anesthetic method do you prefer when performing percutaneous nephrolithotomy for the treatment of kidney stones?

Spinal epidural

Subarachnoid spinal

Local with sedation

Local without sedation

General inhaled

Other (please specify)

19. Do you consider it useful to perform a culture of the percutaneous puncture urine?

Yes
No

20. For the percutaneous tract, what method of dilatation do you commonly use?

Progressive with Amplatz
Progressive with Alken
Dilating balloon
One shot (Amplatz)
Other (please specify)

21. For the percutaneous tract, what French size do you prefer when performing dilatation?

<22 fr
22 fr
24 fr
26 fr
28 fr
30 fr
Other (please specify)

22. Do you usually perform miniperc surgery?

Yes
No

23. What instrument size in Fr. units do you use to create the tract in percutaneous mini renal surgery?

12 fr
14 fr
16 fr
18 fr
20 fr

24. In which cases do you prefer to perform miniperc surgery?

Lithos of 15-20 mm
Less than 15 mm but greater than 10 mm
Calcium hydroxide
Limestones less than 10 mm in the inferior calyx that failed to respond to flexible ureteroscopy
When performing a second percutaneous tract
Lithos greater than 20 mm
Other (please specify)

25. For the fragmentation of the renal calculus, what type of energy do you prefer?

Pneumatic
Ultrasonic
Ultrasonic/Pneumatic
LASER
Other (please specify)

26. At the end of percutaneous nephrolithotomy, do you

Place a nephrostomy catheter
Place a nephrostomy catheter and double "J" ureteral catheter
Place double ureteral catheter "J"
Do not place a nephrostomy catheter or catheter
Other (please specify)

27. Which radiological method do you prefer for evaluating the stone-free status?

Tomography
Ultrasound
Simple abdomen plate
Simple abdomen plate + ultrasound
Other (please specify)

ORIGINAL ARTICLE

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Ureteral access sheaths: a comprehensive comparison of physical and mechanical properties

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ABSTRACT

Introduction: Ureteral access sheaths (UAS) facilitate flexible ureteroscopy in the treatment of urolithiasis. The physical properties of UAS vary by manufacturer and model. We compared three new UAS: Glideway (GW, Terumo, 11/13Fr, 12/14Fr), Pathway (PW, Terumo 12/14F) and Navigator HD (NHD, Boston Scientific, 11/13Fr, 12/14Fr) in the domains of safety characteristics, positioning characteristics, lubricity and radio-opacity.

Materials and Methods: In vitro testing of the three UAS included safety testing- tip perforation force, sheath edge deformation and dilator extraction forces. Positioning characteristics tested included tip bending, stiffness (resistance to coaxial buckling forces), kinking (resistance to perpendicular forces), and insertion forces. Lubricity was assessed by measured frictional forces of the outer sheath. Finally, radio-opacity was tested utilizing fluoroscopic imaging of the three 12F sheaths and inner dilators.

Results: The PW (0.245 lb) and GW (0.286 lb) required less force for tip perforation compared to the NHD (0.628 lb). The NHD sheath edge deformation was mild compared to more severe deformation for the PW and GW. The PW (1.008 lb) required greater force than the GW (0.136 lb) and NHD (0.043 lb) for inner dilator removal. The GW (3.69 lbs) and NHD (4.17 lb) had similar inner dilator tip stiffness when bent, while the PW had the weakest inner dilator tip, 1.91 lbs. The PW (0.271 lb) was most susceptible to buckling and kinking (1.626 lb). The most lubricious UAS was the NHD (0.055 lbs for 12F). The NHD (0.277 lbs) required the least insertional force through a biological model and possessed the greatest radio-opacity.

Conclusions: Comparison of different commercially available UAS in various sizes reveals that there are mechanical differences in sheaths that may play a role clinically. The Terumo sheaths' (GW and PW) were outperformed by the Boston Scientific NHD in simulating safety, ease of use and radio-opacity.

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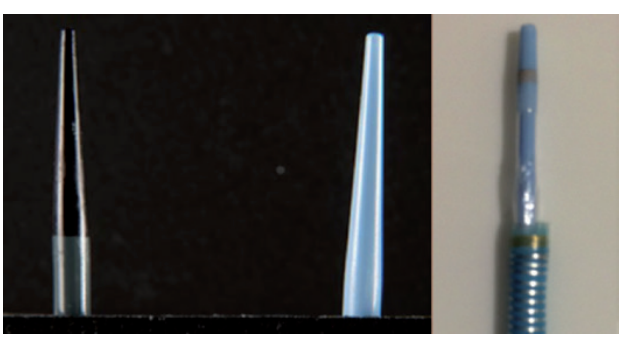
INTRODUCTION AND OBJECTIVES

Ureteral access sheaths (UAS) are commonly used to facilitate flexible ureteroscopy in the treatment of urolithiasis. Reports have highlighted the practical role of the UAS in reducing operative times, allowing multiple passes of instruments, and protecting the ureteroscope (1-4). Further, the UAS has the capacity to improve visualization and reduce intra-renal pressure during ureteroscopy (5, 6). A few studies have observed that UAS can improve stone free rates, though the level of evidence is low (7, 8). Selection of the UAS among the choices of manufacturers and models typically depends on physician familiarity, cost, and size of ureteroscope (9). The physical properties

of ureteral access sheaths vary by manufacturer and model, and these specific characteristics may play a role in their clinical applicability. Dilator tip shape, flexibility, and ease of extraction may affect ureteral safety during sheath advancement and extraction (10). Sheath strength and ability to withstand a diversity of directional forces may impact utility during UAS insertion. In an *in vitro* study, we examined the physical and mechanical properties of the UAS that may impact ergonomics, efficacy, and patient safety. Specifically, we compared three new UAS (Figure-1); the Glideway (GW, Terumo, 11/13F, 12/14F), the Pathway, a distinct balloon-expandable sheath (PW, Terumo, 12/14f), and Navigator HD (NHD, Boston Scientific, 11/13F, 12/14F).

Figure 1 - (From left to right) Boston Scientific Navigator HD, Terumo Glideway, and Terumo Pathway.



MATERIALS AND METHODS

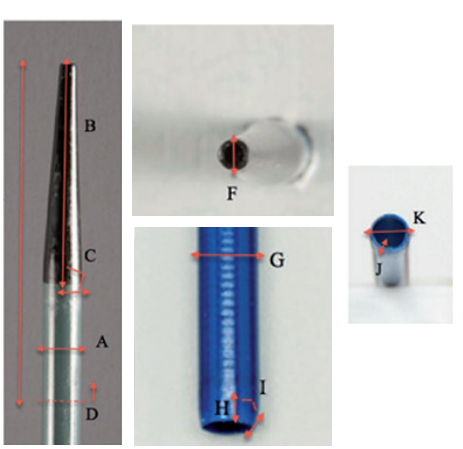
In vitro testing of the Glideway (Terumo, NJ, USA, 11/13F, 12/14F), the Pathway, a balloon expandable UAS (Terumo, NJ, USA, 12/14f), and Navigator HD (Boston Scientific, MA, USA, 11/13F, 12/14F) was conducted to compare physical and mechanical characteristics. We have previously described our methodological techniques for single-wire ureteral access sheaths (10). The GW and NHD were selected as examples of new models of the traditional UAS, with a tapered inner dilator and hydrophilic outer sheath, while the PW represents a unique balloon-expandable sheath design, meant to minimize the sheath diameter. Safety characteristics (tip perforation forces, sheath edge deformation, dilator extraction forces), positioning characteristics [tip bending, stiffness (resistance to coaxial buckling forces), kinking (resistance to perpendicular forces), insertion forces], and lubricity (frictional forces of outer sheath) were examined. Further testing was performed on the PW utilizing an *ex vivo* model (pig ureters) to assess risk for mucosal avulsion for a balloon-expandable device during extraction of the sheath. Tip bending, sheath buckling, dilator removal and frictional forces were measured with an Amplatz Superstiff guidewire (Boston Scientific, MA, USA) inserted through the inner lumen of the inner dilator of the sheath. Inner dilator tip contours and sheaths physical characteristics (Figure-2) were measured using digital calipers (Niko 01407A, China). To assess radio-opacity, fluoroscopic images were taken of the three 12F sheaths and inner dilators. This radio-opacity test was performed utilizing a C-arm (Siemens Arcadis mobile C-arm, Germany) at a distance of 38cm from the intensifier to the sheath with a voltage of 99kV and a tube current of 5.4 mA.

Safety testing

Tip perforation

The inner dilator was mounted on a motorized sliding stage. The dilator end was attached at a length of 10 cm via an alligator clip. The

Figure 2 - Tip contour and sheath characteristics. A) Diameter of inner dilator; B) Taper length of inner dilator; C) Taper grade of inner dilator; D) Portion of inner dilator exposed from sheath; E) Tip Length; F) Leading edge of inner dilator; G) Diameter of outer sheath; H) Taper length of outer sheath; I) Taper grade of outer sheath; J) Thickness of outer sheath; K) Leading edge outer sheath.



alligator clip was fitted to a digital force meter, which continuously measured force (Mark-10 Corp, NY, USA). The stage was advanced until a foil membrane (0.016 mm thickness, standard) was punctured. The maximum force at perforation of the foil membrane was recorded in pounds (Figure-3A). A total of 5 trials were run for each sheath and averaged.

Edge Deformation

The force meter was attached to the sheath at a length of 10 cm. The working end of the sheath was placed directly against a BegoStone®, a synthetic, commercially-available, hard stone phantom made from dental plaster (BEGO USA, Smithfield, RI). The sheath was advanced until a set force was achieved (2.5 lbs). Photos were taken to qualitatively examine outer sheath edge deformation (Figure-3B).

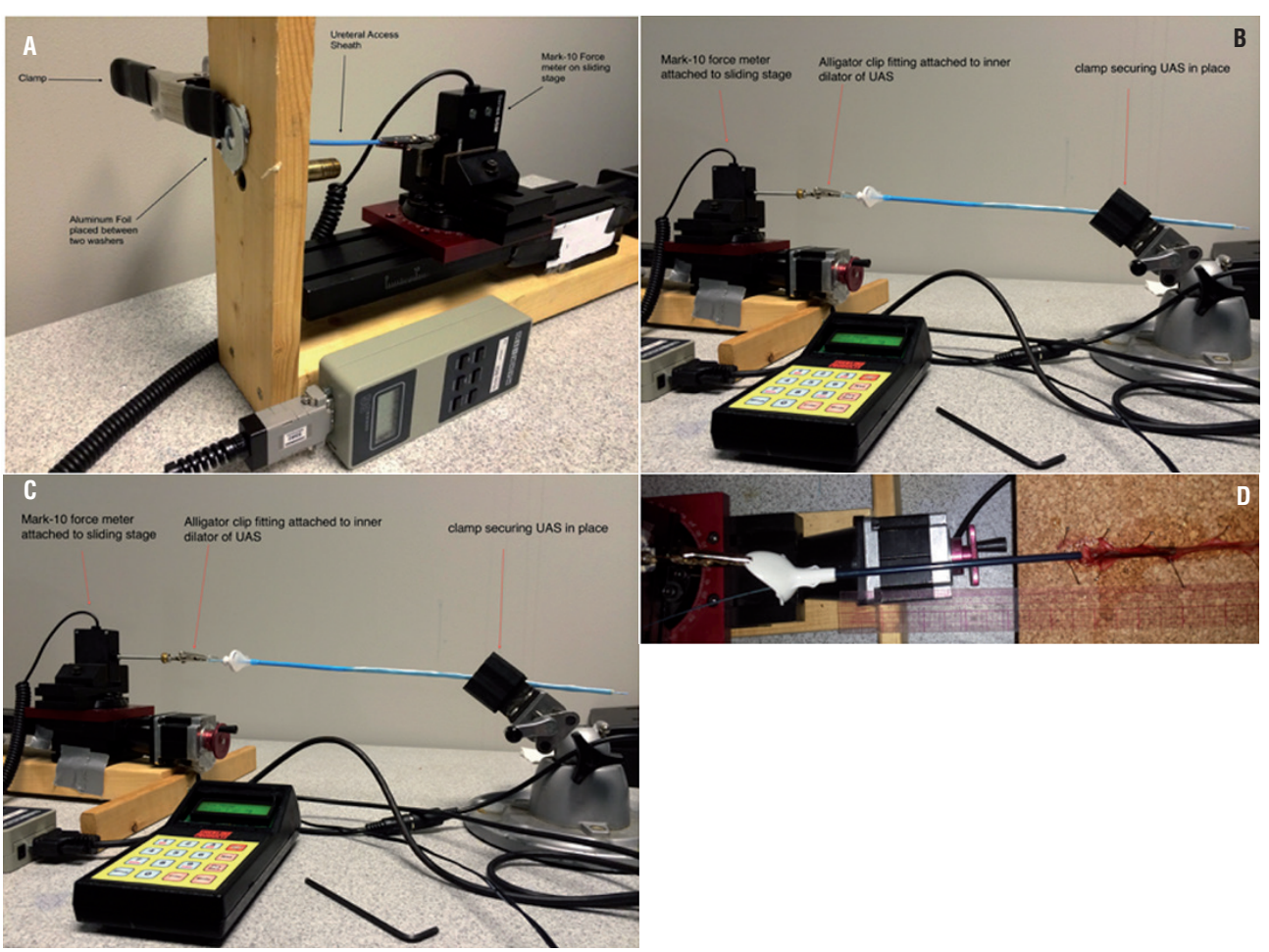
Dilator Removal

The outer sheath was secured at tip end via an adjustable vice and the inner dilator (locking mechanism disengaged) was fixed to a motorized, continuous, digital force meter (Mark-10). The stage was retracted for 7s at 5 mm/s, and average force for a 5s interval was calculated (1-6s) as the dilator was removed (Figure-3C). A total of 5 trials were run for each sheath and averaged.

Extraction Force for Pathway Sheath (Ex Vivo Model)

Superstiff Guidewires were inserted through *ex vivo* ureters (pinned to cork board) and each access sheath was wetted and placed over the guidewire and advanced until in contact with 15 cm of the lumen of the ureter. De-

Figure 3 - A) Tip Perforation; B) Edge Deformation; C) Dilator Removal; D) Extraction Force for Pathway (*Ex* vivo model).



vices were deployed by inflation of the inner balloon, balloon withdrawn and outer sheath left in place for 30 minutes (3 trials each), then attached to a load cell on a stepper motor and extracted at a constant rate, recording the maximum force. Same methods were used while devices were left in place for approximately 60 minutes, for 5 trials each (Figure-3D).

Positioning Testing

Tip Bending

The dilator tip was cut to the length that is typically exposed from the outer sheath. The tip was mounted to a stage and secured to the digital force meter with the alligator clip attachment. The tip was secured in a 2 mm divot in a wooden block and the stage was advanced 1cm recording maximum force (Figure-4A).

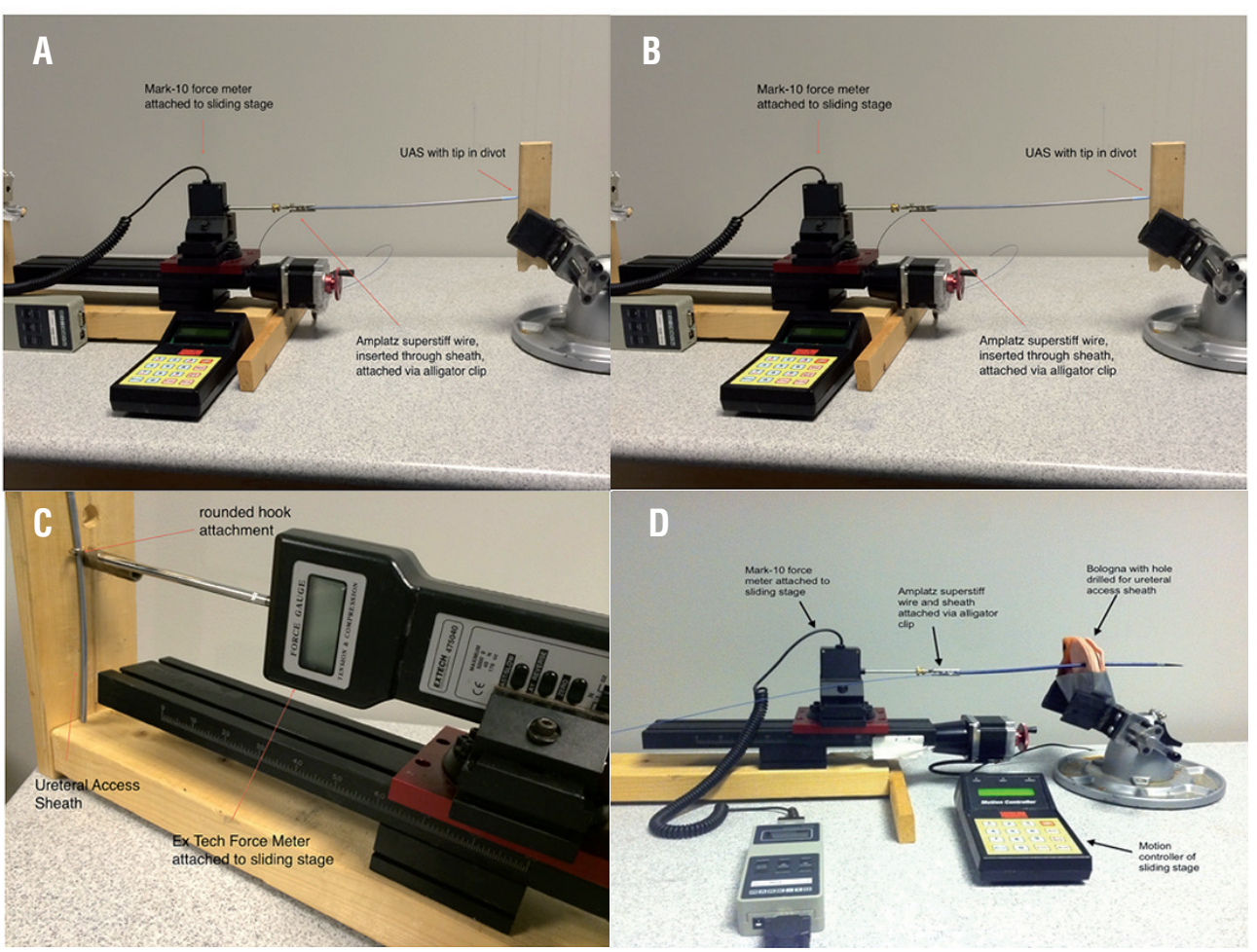
Sheath Buckling

The ureteral access sheath was mounted to a stage and attached to the Mark-10 force meter via an alligator clip at a length of 25 cm from the tip. The tip of the sheath was placed in a 2 mm divot in a wooden block and the stage was advanced 5 cm recording maximum force as the sheath buckled (Figure-4B). A total of 5 trials were run for each sheath and averaged.

Kinking

The ureteral access sheath was secured vertically against a wooden block. A digital force

Figure 4 - A) Tip Bending; B) Sheath Buckling; C) Kinking; D) Insertion force experiment (sheath advanced until midway across UAS).



meter (EX Tech Instruments, 475040, Taiwan), equipped with rounded end attachment was placed perpendicular, flush with the sheath. The rounded end was advanced in 1 mm increments up to 4mm. Maximum force for each increment was recorded as the sheath began to kink (Figure-4C).

Insertion Force with Biological Model

The Amplatz superstiff guide wire was place through the device, and the wire was inserted through the biological model (Oscar Meyer Bologna, 45 mm). The sheath was mounted to a motorized sliding stage and attached to a digital force meter via an alligator clip fitting. The sheath tip was placed flush with the biological model, and the device was advanced at a constant speed penetrating through the biological tissue. The GW and NHD were advanced from tip to mid-shaft, recording maximum force. The PW was advanced in several sections to determine where the greatest force may occur, including 1) until just beyond the tip of the device, 2) from the tip of the device to the middle deflated section, and 3) from the deflated section to the rigid end (Figure-4D).

Frictional Forces with Biological Model

Biological tissue (Oscar Meyer Bologna, 45 mm) was secured via an adjustable vice. Sheaths were soaked in water and inserted perpendicularly through the biological model up to 3 cm from the proximal end for the start of the experiment. The sheath was then retracted for 7s at 5 mm/s while attached to motorized, continuous, digital force meter (Mark-10). Average force was calculated for 5 seconds of the test (1-6s).The PW sheath was extracted as designed; that is, the balloon was inflated after insertion through the biological model, the balloon was then removed, and the extraction force of the remaining outer sheath was measured (Figure-4D).

STATISTICAL ANALYSIS

Descriptive statistics were calculated for all sheaths in each experiment; average forces and standard deviation are displayed in Table-1. UAS were divided into groups based on inner diameter (12F and 11F). Student *t* tests were performed to compare two individual sheaths of the same size (12/14F, 11/13F) for all experiments, and ANOVA was used to compare 3 or more sheaths. Statistical significance was determined at $P<0.05$.

RESULTS

Tip Contour and Sheath Characteristics

Tip contour and sheath measurements are displayed in Tables 1 and 2. The GW inner dilator tip had the longest taper length and most gradual taper grade, making it the sharpest of the sheaths. The NHD inner dilator had the greatest taper grade, making it blunter than the GW and the PW. The diameter of the NHD's outer sheath was larger than both the PW and the GW. The PW's outer sheath was the thickest, likely due to the balloon-distension design, while the GW was the thinnest. The NHD outer sheath had a mild taper, while the Terumo GW and PW sheaths' did not.

Table 1 - Outer Sheath Characteristics.

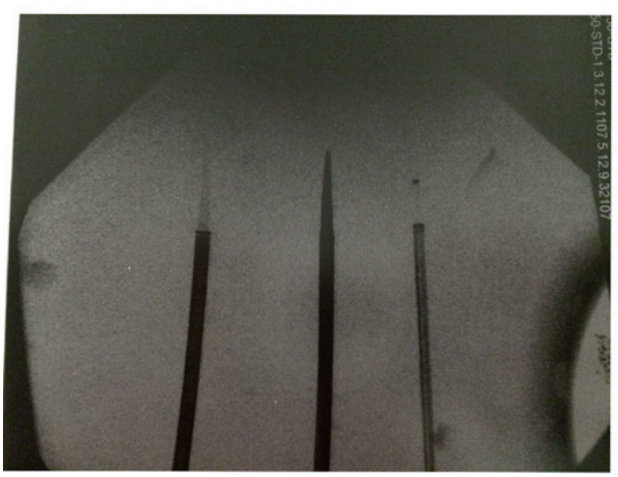
Outer Sheath	Diameter (mm)	Taper length (mm)	Taper grade	Taper grade (degrees)	Tip length (mm)	Leading edge (mm)
GW 12	4.68	n/a	n/a	n/a	0.25	4.24
PW 12	4.2	n/a	n/a	n/a	0.32	4.86
NHD 12	4.82	2.85	0.065	3.714	0.27	4.45
GW 11	4.33	n/a	n/a	n/a	0.25	3.85
NHD 11	4.43	2.12	0.066	3.778	0.3	4.15

n/a = not available

Table 2 - Tip Contour Measurements.

Inner Dilator	Diameter (mm)	Taper length (mm)	Taper grade	Taper grade (degrees)	Tip length (mm)	Leading edge (mm)
GW 12	4.02	26.72	0.041	2.38	28.66	1.8
PW 12	1.53	8.21	0.045	2.58	48.8	1.44
NHD 12	3.97	21.25	0.056	3.19	25.5	1.6
GW 11	3.72	24.96	0.040	2.32	26.83	1.7
NHD 11	3.61	19.6	0.049	2.83	24.78	1.7

Figure 5 - Radio-opacity. from left to right: GW, NHD, PW.



Radio-opacity (Figure 5)

The NHD was uniformly radiopaque, and the entire inner dilator tip was clearly visible on X-ray. The GW had a radiopaque marker at the distal end of its outer sheath, but the leading edge actually extended beyond this marker. In addition, the GW's inner dilator was barely visible on X-ray. The PW also had a distal outer sheath marker, with a small portion of the sheath's leading edge extending beyond this marker. Unlike the GW, the PW's inner dilator also had a radiopaque marker at the distal tip, although the remainder of the inner dilator was difficult to visualize on X-ray.

Safety Characteristics- Table-3

Tip Perforation

The Terumo sheaths consistently required significantly lower foil perforation forces (GW, 0.398 lbs for 11/13f, and 0.286 lbs for 12/14f) than the NHD (0.67 for 11/13f, 0.628 lbs for 12/14f, $p<0.05$). Of the 12/14F sheaths, the PW required the least perforation force ($p<0.05$), and required approximately 1/3 of the perforation force of the NHD (0.245 lbs s 0.628 lbs, $p<0.05$), but was not significantly different than the GW (0.286, $p=0.270$).

Dilator Removal

The PW sheath had the largest force for dilator removal (1.008 lbs), requiring >20 times more force than the NHD (0.043 lbs, $p<0.05$) and 7 times more force than GW (0.136, $p<0.05$). The GW sheath also required significantly greater force for dilator extraction than the NHD. This was consistent across both sheath sizes, with the GW 11/13F requiring 7 times more force (0.437 lbs) than the NHD 11/13F (0.060 lbs, $p<0.05$), and the GW 12/14F. Frequiring over 3 times more force (0.136 lbs) as the NHD 12/14F (0.043 lbs, $p<0.05$).

Edge Deformation

The PW exhibited severe deformation of its edge at a set force of 2.5 lbs. The GW exhibited moderate-severe deformation of its edge at a set force of 2.5 lbs, while the NHD showed only mild deformation at the same force. This occurred at both sheath sizes. Images of deformed sheath edges are displayed in Figures 6A-C.

Extraction Force for Pathway Sheath (Ex Vivo Model)

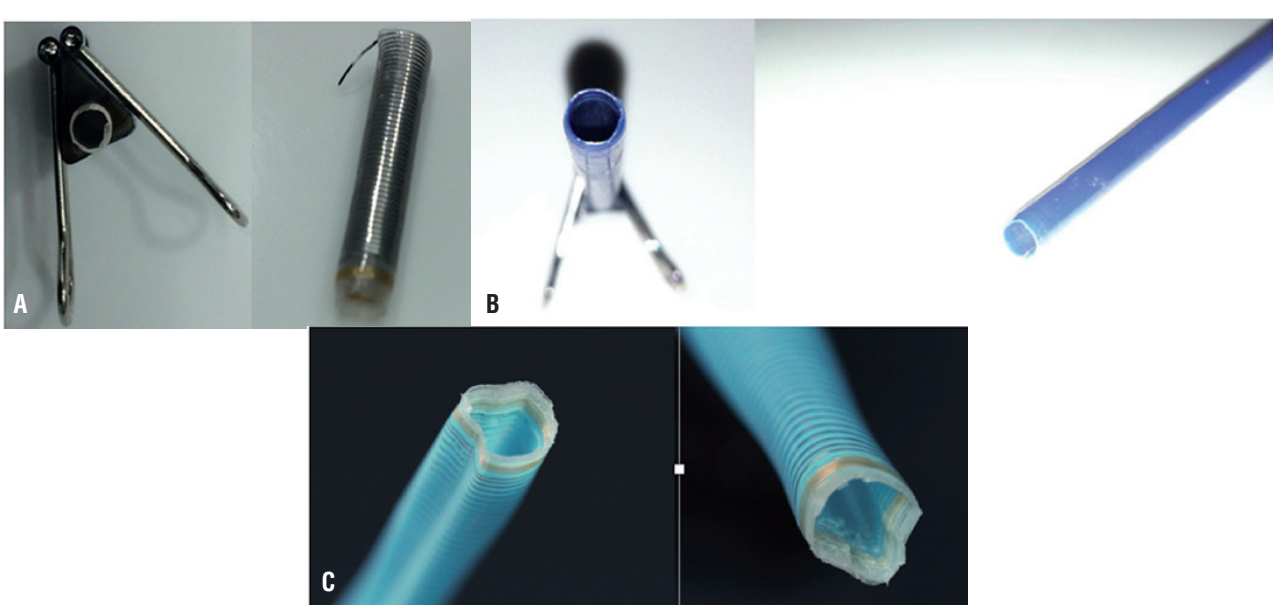
After the PW was left in place for 30 min. in the pig ureter, it required 0.010 lbs for extraction. After 60 minutes, PW required 0.156 lbs for

Table 3 - Mean forces (lbs) for safety, positioning and lubricity testing.

	Experiment	GW 11	NHD 11	t Test p value	GW 12	NHD 12	PW 12	ANOVA Test p value for 12F
Safety	**Tip Perforation**	0.398±0.252	0.67±0.103	0.008*	0.286±0.094	0.628±0.204	0.245±0.067	$9.73X10^{-7}$ *
	Edge Deformation	moderate-severe deformation	mild deformation	n/a	moderate-severe deformation	mild deformation	severe deformation	n/a
	Dilator Removal	0.437±0.013	0.060±0.020	$1.30x10^{-15}$ *	0.136±0.005	0.043±0.020	1.008±0.305	$4.27x10^{-6}$ *
Positioning	**Tip Bending**	3.745±0.380	4.381±0.779	0.076	3.693±0.243	4.165±0.664	1.91±0.452	$3.84x10^{-8}$
	Buckling	0.889±0.022	1.031±0.039	$1.035x10^{-7}$ *	1.058±0.023	1.102±0.079	0.271±0.030	$4.69x10^{-25}$
	Kinking	4.389	4.137	0.867	3.628	3.767	1.626	0.086
Lubricity	**Insertion (biological model)**	—	—		0.467	0.277	0.344	$1.42x10^{-5}$*
	Sheath Extraction, biological model (Friction)	0.079±0.010	0.059±0.009	0.004*	0.090±0.031	0.055±0.009	0.260±0.072	$3.53x10^{-7}$ *

* = p-values have no units

Figure 6 - A) Glideway edge deformation; B) Navigator HD edge deformation; C) Pathway edge deformation.



extraction from the ex vivo model. At both time points, apparent mucosal avulsion occurred for this sheath (Figure-7).

Figure 7 - Pig Ureteral Avulsion with Extraction of Pathway.

Positioning- Table 3

Tip Bending/Flexibility

The PW 12F had the weakest inner dilator tip, requiring approximately half the force (1.91 lbs) of the other two sheaths (GW 3.69 lbs, NHD 4.17, $p<0.05$). The GW and NHD inner dilator tips were equally stiff, requiring similar forces for the tip flexibility experiments at both sizes, with the GW 11/13F and 12/14F requiring 3.745 and 3.693 lbs, respectively and NHD 11/13F and 12/14F requiring 4.381 and 4.165 lbs, respectively ($p=0.153$).

Shaft Buckling

The PW sheath was most susceptible to shaft buckling/bending forces, requiring 1/4 of the force (0.271 lbs) of the other sheaths for this experiment (GW 12 1.058, NHD 12 1.202, $p<0.05$). The two Terumo sheaths required significantly different forces when compared as a pair ($p<0.05$). The GW 12/14F and NHD 12/14F shafts were equally resistant to coaxial forces, requiring similar forces for sheath buckling (GW 1.058 lbs, NHD 1.102 lbs, $p=0.11$). However, for the 11/13F sheaths, the NHD was significantly stronger against coaxial forces, requiring 1.031 lbs for sheath buckling, while the GW required 0.889 lbs ($p<0.05$).

Kinking

The PW required the least amount of force for kinking (1.626 lbs), and this was significantly less force than the NHD (3.767 lbs, $p<0.05$), but not significantly less than the GW (3.628 lbs, $p=0.118$). Both GW and NHD sheaths were equally resistant to kinking (perpendicular forces), with the GW 11/13F and 12/14F sheaths withstanding 4.389 lbs and 3.628 lbs, respectively and the NHD, 4.137 and 3.767 lbs, ($p=0.867$ for 11/13f and $p=0.92$ for 12/14f).

Insertion Force Through Biological Model

The three sheaths required significantly different mean forces for insertion through the biological model (ANOVA $p=1.42x10^{-5}$). The GW 12 required significantly greater force (0.468 lbs) than both the PW 12 (0.344 lbs, $p=0.002$) and the NHD 12 (0.277 lbs, 4.29x10-5). The NHD required significantly less force compared to the PW ($p=0.02$).

Lubricity- Table 3

The lubricity testing revealed that the NHD sheath consistently required significantly lower frictional forces in a biological model than the GW (0.059 vs. 0.079 lbs, $p<0.05$ for 11/13F sheaths and 0.055 and 0.090, $p<0.05$ for 12/14F sheaths) and the PW (0.230 lbs vs. 0.055 for 12f, $p<0.05$). In fact, the PW required 4 times more frictional force than the NHD.

DISCUSSION

Though the use of ureteral access sheaths remains a debated topic in endourology, there are many aspects of flexible ureteroscopy that may be facilitated with their use. Several

studies have shown that irrigation pressures conducted to the renal pelvis and throughout the kidney are lower during ureteroscopy with a UAS than without a UAS (5, 6, 11). Although the effects of this have not been fully outlined, reduced pressures may have the capacity to prevent the dissemination of infection during treatment of struvite stones as well as in cases of stones with secondary infection (5). The UAS also allows sustained access, permitting easier insertion and extraction of various instruments, and can improve visualization of the procedure (1, 8, 9). It has been shown that UAS use may positively affect outcomes following flexible ureteroscopy (1). In one retrospective study on 256 patients, the UAS resulted in improved stone free rates on IVU or CT at two months following stone procedure (8). In addition, in several other studies, UAS use has been shown to reduce operative time, cost and morbidity (1, 8, 12). Anuway, the studies supporting the use of UAS have low level (3b) of evidence. UAS are available in a variety of sizes and designs and have evolved to fit the ureteroscope. Most UAS have a hydrophilic coating, radio-opaque markings, and a tapered tip with a smooth transition between dilator and outer sheath.

While ureteroscopy is considered a valuable tool in the management of nephrolithiasis, it can result in ureteral injury (13). In a large, single-center study, the overall intra-operative complication rate of ureteroscopy was 3.7%, false passage rates were 1%, and morbidity from ongoing hematuria and renal colic was 2.04% and 2.23%, respectively (13). While the UAS has the safety advantages of improved visualization, reduced renal pressures, and simplified access, the use of a ureteral access sheath does not come without inherent risk of harm. Safety concerns include the risk of ureteral perforation or avulsion, and it has been proposed the UAS use may increase surgical costs, as UAS use mandates use of extra equipment (wires and ureteral stents). In a prospective study of 359 patients undergoing URS, Traxer and Thomas systematically graded and assessed ureteral wall injury resulting from UAS insertion, and found that up to 46.5% of patients had some type of ureteral wall injury (14). While 13.3% of these were "severe" (involving the ureteral smooth muscle), the clinical relevance of the minor injuries is not fully understood (13). As such, it is critical that new sheaths be evaluated systematically for physical characteristics that may impact clinical performance, risk, and outcomes. Previous *in vitro* studies have identified clinically relevant mechanical properties pertaining to UAS usability, such as resistance to buckling and kinking forces, and lubricity (11, 15). Here, we apply these principles to a new set of ureteral access sheaths in order to assess safety characteristics and clinical differences among new equipment.

Although most sheaths have a basic, stiff inner dilator with a flexible tip, Terumo PW has a distinct inner balloon-inflatable model, designed with a smaller distal sheath diameter (deflated balloon) for insertion. Once advanced up the ureter, the balloon is then inflated, and the inner dilator is then removed as with other sheath designs. The intent of this design was to decrease insertion forces and the risk of perforation with a smaller caliber sheath at time of insertion. However, our study demonstrates that insertion forces are similar to traditional sheaths and perforation forces are lower (i.e. the risk of perforation is higher with less force). As such, the PW design does not appear to provide a safety advantage. Instead, this study demonstrates a safety hazard – with a larger extraction force leading to a higher risk of mucosal avulsion.

The Terumo Sheaths (PW and GW) consistently required less force for tip perforation, for both sizes of sheaths. This may be explained by the observation that the inner dilator tips of both the GW and PW were indeed sharper (shallower grade). As such, the GW and PW tips carry a risk of ureteral perforation at lower insertion forces.

The PW required significantly greater force than both the GW and the NHD for inner dilator removal. Mechanical difficulty with dilator extraction could introduce unnecessary tip displacement within the ureter. Although the forces may be small, these unduly large di-

fferences in forces (PW >20 times the force of the NHD) implies key differences in usability and design with regard to this step of the procedure. The clinical impact of these differences is unknown. Here, the NHD has the advantage in that its inner dilator can be removed more smoothly.

Safety parameters regarding the PW were further outlined in our *ex vivo* experiment, where outer sheath extraction was evaluated following placement for 30-60 minutes in pig ureters, revealing that gross mucosal avulsion occurs with sheath extraction. Since the extraction forces increased from 30 to 60 min., it is possible that the propensity for ureteral injury increases with duration of surgery.

As displayed in Figures 6A-C, the Terumo sheaths suffered the greatest mechanical damage when impacted against the pseudo calculus, with the PW showing severe deformation and the GW showing moderate to severe deformation, while the NHD only had mild-moderate damage. This experiment simulates an intra-operative attempt to basket a stone that is too large to pass easily through the ureteral access sheath. A sheath that does not uniformly tolerate forces at its edges is more prone to deformation in this setting. The greater edge destruction may correspond to a structural difference in sheath edge, such that a force against the edge does not disperse uniformly. Indeed, we found that the GW's sheath edges were slightly thinner than the NHD's. In theory, the force applied by an impacted stone at the end of the sheath can distort the sheath edges. It is possible that the significant edge damage rendered by the stone for the Terumo PW and GW versus the NHD could prevent extraction of other stones during the procedure, and if severe could disrupt the urothelium during sheath extraction.

In our experiments, the NHD 11/13F sheath was more resistant to buckling than the GW 11/13F sheath. Clinically, this is important during the initial insertion of the sheath into the ureter (12). We can infer that the small-diameter NHD sheath may perform better in the case of a difficult insertion into a tight ureteral orifice and would less likely buckle in the bladder.

Newer, more durable ureteral access sheaths have been designed with metal coiling within the sheath to minimize kinking during insertion (15). Both the GW and NHD sheaths performed equally well in response to kinking forces, withstanding large forces with minimal damage. Resistance to kinking helps minimize the risk of extrinsic compression at the bladder neck or point of ureteral narrowing (12). However, the PW sheath was significantly more susceptible to kinking forces than the NHD. Inherently, the PW requires a malleable outer sheath design to allow expansion with balloon inflation; as such, the resistance to kinking is lower when compared to the NHD, which possesses a stainless steel coil reinforcement for added strength. A limitation of our study is that not all commercially available ureteral access sheaths were selected for comparison.

The insertion force experiment was designed to compare both ease of sheath placement and propensity for ureteral injury during sheath advancement. The NHD had the lowest maximum insertion force while traversing our biological model, while the GW required the largest insertion force; the PW's force was intermediate. It is possible that the NHD's coating and smoother transition between dilator transition between inner dilator and outer sheath provide for lower insertion forces. Indeed, the NHD is the only sheath available commercially that had a mild taper of the outer sheath's leading edge, likely minimizing the excess force introduced by sudden changes in sheath caliber. The GW's large insertion forces may result from difference in outer coating, or alterations in dilator-sheath transition; as this sheath did not have an outer sheath taper according to our measurements. This quality predisposes the GW to minor mucosal injuries during sheath insertion. The PW's small sheath profile and balloon-inflation mechanism is designed to depend on radial, or circumferential dilation of the ureter in lieu of introducing axial shearing forces, thereby reducing insertion forces, in theory. Here, we demonstrate again that this design does not minimize insertion forces as it claims to, as they are still considerably higher than the NHD. This difference is likely due to the stiffer tip and shaft of the PW.

The friction experiment was designed to assess ease of advancement and smooth handling of the UAS. We hypothesized that the ease of insertion would also correspond to the slipperiness of the outer sheath, as assessed in the friction testing. Indeed, the NHD also required the lowest frictional forces. NHD required significantly less frictional force at both sheath sizes than the GW, and the NHD 12F required 1/4 of the frictional force of the PW 12F. The slippery quality of the NHD sheath may provide for easier, smoother advancement compared to the other sheaths. Since the frictional forces were quite small, the clinical impact of differences in lubricity is unclear.

The differences in radio-opacity among the sheaths may additionally affect ease of sheath placement. While the outer sheath markings of the Terumo sheaths may aid in guiding placement, we are concerned about the poor visibility of the inner dilator tip and the outer sheaths' distal leading edge for both the GW and PW. A poorly visualized dilator tip may lead to unintentional mucosal, renal pelvic or parenchymal injury during placement. The uniformly radiopaque quality of the NHD may aid in placement, ensuring both outer sheath and inner dilator are easily visualized.

CONCLUSIONS

Comparison of different commercially available UAS in various sizes reveals that there are mechanical differences in sheaths that may play a role clinically. The Terumo sheaths' (GW and PW) were outperformed by the Boston Scientific NHD in simulating safety, ease of use and radio-opacity. The PW's balloon design and smaller distal sheath caliber has no benefit in terms of sheath insertion forces and may pose a risk of mucosal avulsion.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

CONFLICT OF INTEREST

None declared.

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Evaluation of urodynamic parameters after sling surgery in men with post-prostatectomy urinary incontinence

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ABSTRACT

Objective: To evaluate urodynamic alterations after sub-urethral sling surgery (SSU) in patients with post-prostatectomy urinary incontinence (PPUI).
Materials and Methods: We evaluated data of 22 patients submitted to radical prostatectomy (RP) or transurethral resection of prostate (TURP) that presented post-surgical urinary incontinence and were treated with SSU implant in a pilot study previously performed in our institution.
Methods: Those patients with PPUI were evaluated by urodynamic exam (UD) before and after surgery, and the parameters were compared, including uroflow, cystometry and micturition study. Exclusion criteria included patients without pre-operatory urodynamic study, those with urethral stenosis, those not healed of prostate cancer, patients without clinical conditions to be submitted to urodynamic study and those with severe neurological diseases or that refused to sign the consent form. Results were analyzed statistically by Fisher, Wilcoxon or Mann-Whitney tests.
Results: During free uroflow, none parameters showed any statistical significant differences. During cystometry, there were also no statistical differences and the same was observed at pressure versus flow study; the exception was at maximal flow detrusor pressure (PdetQmax), that was lower at post-operatory (p=0.028). In relation to the presence of urinary dysfunctions associated to PPUI, we observed a significant reduction of detrusor overactivity (p=0.035) in relation to pre-operatory period.
Conclusion: SSU surgery significantly reduced detrusor overactivity and PdetQMax; however, there were no alterations of other evaluated urodynamic parameters.

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INTRODUCTION

Post-prostatectomy urinary incontinence (PPUI) is a common complication of surgical treatment of patients with prostate cancer or benign prostatic hyperplasia and cause a negative impact on quality of life (1).

PPUI is defined by International Continence Society (ICS) as an involuntary loss of urine during strain following prostatic surgery, that can be single or associated to other vesical dysfunctions (2-4).

The main and more prevalent cause of PPUI is radical prostatectomy (RP), and its incidence varies from 2.5% to 67% (5, 6).

Some studies show that the main urethral and vesical dysfunctions that occur after RP include: intrinsic sphincter deficiency, detrusor overactivity, loss of complacency and loss of detrusor contractility (7, 8).

PPUI treatment includes conservative measures (physiotherapy, for example), sub-urethral sling surgeries (SSU) and artificial urinary sphincter (AUS). Conservative treatment speeds recovery

of slight PPUI in the first months following surgery, and there is indication of surgical treatment for patients without improvement (9). The most efficient surgical treatment is AUS implant, but with higher costs. Also, some patients decide for the use of a mechanical device (10). In that context, SSU surgeries were proposed and nowadays they include two types, according to their mechanism of action: those adjustable and compressive, and those functional or non-compressive (11).

There are many controversial and uncertain aspects regarding those action mechanisms of SSU; they have been studied by urodynamic exams and also by magnetic nuclear resonance of pelvis, to evaluate position and length at membranous urethra (12). In relation to urodynamic evaluation, there are few reports of the whole exam, and the authors choose to report only some urodynamic data. Therefore, new studies are justified for better evaluation of SSU effects (13).

We analyzed patients submitted to SSU by urodynamic studies, to improve understanding of the effects of surgery in the main parameters of the exam, trying to identify potential prognostic factors or action mechanisms.

OBJECTIVE

To evaluate urodynamic alterations caused by SSU surgery in patients with post-prostatectomy urinary incontinence.

MATERIALS AND METHODS

This is an observational and retrospective study of 22 patients previously submitted to SSU in our institution. From December 2010 to June 2013, all patients with PPUI submitted to SSU surgery were invited to participate. Age varied from 50 to 74 years (median 66 years); all patients were submitted to urodynamic study before and after surgery. Pre-operatory exam was performed after at least 8 months of history of PPUI and at least 6 months after SSU surgery. Patients were part of another pilot study that compared two SSU techniques: compressive and adjustable versus non-compressive (1). In summary, patients with any intensity of PPUI were randomized and prospectively treated with SSU. In that study, there were no significant statistical differences of objective criteria (pad test, use of sanitary napkins) but Advance® sling had better subjective results (satisfaction).

Inclusion criteria: patients that signed the Free Consent Form, patients no irradiated, without urethral stenosis and/or previous stenosis but surgically treated by SSU, those still with PPUI or healed by SSU surgery. Exclusion criteria: patients without pre-operatory urodynamic study, those with urethral stenosis not treated, with active prostate neoplasia, without clinical conditions for the procedure or with severe neurological diseases.

For this study, PPUI was defined as any urinary loss confirmed by urodynamic study and/or pad test that promoted the patient to desire treatment.

The following slings were used: Argus T® - Promedon – Argentina (compressive and adjustable) or Advance® - A M S - USA (non-compressive). They were available when our Public Institution concluded bidding process.

All patients were submitted to urodynamic study, that included three phases: uroflow (maximum flow (QMax), post-micturition residual urine, urinary volume), cystometry (maximum cystometric capacity (MCC), first micturition desire, volume at normal micturition desire, urinary loss pressure (VLPP) and flow/pressure study (detrusor pressure at maximum flow (PdetQmax), maximum flow (Qmax), urinary volume and post-micturition residual urine). The following equipments were used: Alacer- Uranus II and Dynamed- Dynapack MPX816 urodynamic devices, that were managed according to the recommendations of the International Continence Society (ICS) (Schafer (14, 15)).

The first phase of the study was free uroflow: when the patient had a moderate desire to urinate, he was oriented to urinate freely in the equipment and, following micturition, the computer program provided a graphic for analysis.

In the second phase of the exam, cystometry, the patient was positioned in a bed in supine position, for genital region asepsis. Five to 10 mL of lidocaine gel was introduced in the urethra and two urethral catheters were positioned (6 and 8Fr)

and fixed at the penis, and the urinary residue was measured. Next, a rectal catheter was introduced for measurement of abdominal pressure. Lastly, the patient was seated in an appropriated chair and the catheters were attached to the equipment and the cystometry was initiated.

Sterile distilled water was introduced in the 8Fr urethral catheter and the filling was monitored; it was asked to the patient inform the first micturition desire, the normal desire and the maximum desire. When the last was reached, he was asked to cough (strain maneuver) to evaluate the presence of urinary loss. If there were no losses, the 8Fr catheter was removed and the stress maneuver was again performed to verify any urinary loss.

Next, the patient was asked to urinate for the flow/pressure study; after that, residual urine was measured and the catheters were removed, ending the exam.

Following the urodynamic study, the patients received antibiotic prophylaxis with norfloxacin 400 mg every 12 hours for three days, and were clinically followed up to identify possible signs of secondary infection.

The results were statistically analyzed by the Fisher, Wilcoxon and Mann-Whitney tests, with a significant level of 5%.

The study protocol was approved by the Ethical Research Committee of the Institution.

RESULTS

All 22 patients with PPUI submitted to SSU surgery were included in the present study. Table-1 shows median age, type of prostate surgery and median time from prostatectomy to sling surgery.

Two patients died due to acute myocardial infarction; one after six months of the procedure and the other after 12 months, both without any relation to SSU surgery.

After at least six months of surgery for PPUI correction, 4 of the 22 patients with pre-operatory UD were excluded, since 2 died and 2 developed urethral stenosis. Of those, 3 had been submitted to Argus T SSU® and one to Advance® implant.

Table-2 shows the urodynamic parameters during free uroflow, cystometry and flow/pressure study; the only parameter with significant difference

Table 1 – Time after prostate surgery, age and type of SSU surgery.

	Argus T®	Advance®
Age (medium)	62.55 (52 to 74 years)	62.09 (50 to 71 years)
Time after prostate surgery (medium)	53.82 (8 to 98 months)	52.18 (12 to 187 months)
Prostate Surgery	10 RP / 1 TURP	11 RP

RP = radical prostatectomy; **TURP =** transurethral ressection of prostate

Table 2 – Bladder dysfunction: comparison of pre and post-operatory.

	Pre	Post	p* (pre x post)
Complacence Deficit	4(18%)	2(10.5%)	0.180
Detrusor overactivity	10(45.4%)	2 (10.5%)	0.035*
Lowered maximum cystometric capacity	6(27.2%)	4 (21%)	0.414
Hypocontractility	2(9%)	6 (31.5%)	0.180
Obstruction	3 (13.6%)	3 (15.7%)	1.000

p - descriptive level of probability at non-parametric Wilcoxon test.

was detrusor pressure at maximal flow (PDetQ-max) ($p<0.028$).

In relation to the presence of urinary dysfunction, it was observed a reduction of detrusor overactivity from 45.4% to 10.5% of patients (Table-3).

After surgical procedures, the following results were observed: among patients submitted to SSU Advance® - Qmax varied from 2.6 to 30 cmH_2O and the urinary residue varied from 0 to 42 mL. In relation to SSU Argus T, Qmax varied from 0 to 23.3 mL/s and Pdet/Qmax from 0 to 38 cm H_2O, and the urinary residue varied from 0 to 300 mL.

When SSU pre and post-surgical results were singly compared, differences were not significant, except Pdet/Qmax of Advance® patients, that presented a statistical significant reduction.

When the results of both SSU types were compared (Argus T® x Advance®) it was not also observed any statistical difference.

DISCUSSION

Post-prostatectomy urinary incontinence (PPUI) is a complication of prostatic surgeries (RP or TURP). Many etiologic factors are involved, but they are not well elucidated (14).

Literature shows that the main cause of PPUI is sphincter deficiency, but that may be associated to any kind of urinary dysfunction (for example, detrusor overactivity) (2). Méndez Rubio et al. (16) suggested that these findings probably reflect a secondary urinary dysfunction caused by bladder denervation during surgery. Stavropoulos et al. (17) considered age as an important factor, since it causes histological changes of bladder muscle and connective tissue. The alterations, associated to those produced by radical prostatectomy cause changes in sphincter function that can be identified by some urodynamic parameters (sphincter deficiency, detrusor overactivity, hypocontractility, etc) and can cause incontinence. Median age of those studied patients was 62 years, and being not that old, we believe that this is not such a so prevalent factor for PPUI.

Urinary dysfunction may be associated or not to sphincter deficiency, as observed by Jura et al. (10) in 15% of patients with PPUI. Barniou et al. (18) observed that urinary dysfunction may be observed even after prostatic surgeries, in a study where they reported persistence of hypocontractility in 25% and complacence deficit in 28.1% after 3 years. Similarly to our results, after more than 12 months of RP, it was observed a complacence deficit in 18% of patients and hypocontractility in 9% and it was not clear if those occurred due to bladder dysfunctionalization secondary to PPUI or to other factors.

In the last few years, SSU were designed and reformulated as an option of AUS 800® artificial sphincter, due to their promising results and lower costs, that consolidated them as an option for the treatment of PPUI (1, 19).

In relation to what literature shows regarding action mechanisms of SSU, it is suggested that AdVance® sling mash may modify the dynamics of bulbar urethra (repositioning and increase of rabdosphincter length) resulting in functional improvement of sphincter (16); differently, implant of SSU Argus T® would change angulation and urethral compression (20). Therefore, Advance Sling® doesn't have a compressive action, as observed by Bauer et al. (21); they evaluated the pre and post-surgical urodynamic parameters of patients treated with Advance® sling and observed that residual urine after initial free flow did not alter after treatment and postulated that this kind of sling did not produce a compressive effect. This non-obstructive effect was also proven by Ullrich and Comiter (4) and Davies et al. (22), that did not identify any significant change of maximum flow, pressure at maximum flow and post-micturition urinary residue.

Although literature assigns a compressive effect to Argus T Sling, Rehder et al. (23) showed that maximum flow during flow/pressure study did not alter significantly at post-operatory period. The authors believe that it is caused by the big angle produced by the sling, providing a limited perpendicular strength. The movement does not "strangle" the urethra and, therefore, it is less

Table 3 - Comparison of pre and post-operatory urodynamic results.

Variable	n	Medium	sd	Minimum	Maximum	P25	Median	P75	p(<0.05) *
Qmax (free flow) (mL)									
Pre	19	11.12	13.76	4.00	55.20	0.00	5.90	19.00	0.877
Post	19	11.58	8.88	0.00	32.70	4.70	11.00	17.60	
Post micturition urinary residue (free flow) (mL)									
Pre	19	8.16	20.90	0.00	90.00	0.00	0.00	10.00	0.503
Post	19	13.68	27.28	0.00	100.00	0.00	0.00	20.00	
VLPP (cmH_2O)									
Pre	18	51.50	38.56	0.00	140.00	15.70	50.00	78.75	0.356
Post	18	74.00	73.64	0.00	200.00	0.00	62.00	155.50	
Maximum cystometric capacity (mL)									
Pre	18	333.44	77.01	158.00	450.00	298.75	335.50	400.00	0.052
Post	18	289.44	91.30	123.00	403.00	202.25	300.00	391.25	
Qmax (f X P) (mL/s)									
Pre	18	17.12	12.19	3.00	44.00	8.60	13.00	24.65	0.067
Post	18	10.34	6.69	0.00	23.30	4.98	9.65	15.35	
Residual urine (FxP)(mL)									
Pre	18	51.11	88.99	0.00	300.00	0.00	5.00	58.75	0.507
Post	18	33.50	72.27	0.00	300.00	0.00	4.00	40.50	
P. Det. Qmax(cmH_2O)									
Pre	18	27.76	14.70	11.00	55.00	15.50	24.90	36.95	0.028*
Post	18	15.10	12.20	0.00	38.00	3.50	15.90	25.85	
Urinary volume at free flow (mL)									
Pre	17	153.32	190.92	22.20	657.50	35.10	75.00	238.50	0.102
Post	17	206.31	175.34	42.20	699.00	62.00	221.00	312.60	
Bladder volume at normal desire (mL)									
Pre	19	245.37	85.42	13.00	365.00	200.00	278.00	300.00	0.344
Post	19	216.53	85.24	0.00	390.00	167.00	220.00	261.00	
Urinated volume at flow/ pressure study (mL)									
Pre	16	338.46	89.56	132.00	388.00	275.75	317.50	379.63	0.173
Post	16	242.38	98.44	123.00	490.30	194.15	286.90	317.23	

Qmax = maximum flow; **VLPP =** urinary loss pressure; **n =** number of sample; **sd =** standard deviation; **P25 =** value that is preceded by 25% of values; **P75 =** value that is preceded by 75% of values; **p =** descriptive level of probability at non-parametric Wilcoxon test.

possible to cause tissue ischemia, lowering the chance of obstruction and atrophy.

The results observed in our study of patients submitted to Argus T cannot be considered significant for obstruction and also had no statistical difference. The only parameter with a significant difference (for less) was Pdet/Qmax: 27.76 cmH_2O pre-op to 15.10 cmH20 post-op (p=0.028), opposing the hypothesis of obstruction or urethral compression. The small number of patients studied does not allow a definitive conclusion of this finding. One hypothesis is that SSU are not really compressive, since in some healed patients Pdet/Qmax did not raise; another possibility is that in more adequate samples with a larger number of patients, urodynamic alteration will be more clear. Literature is also rare in this aspect and new studies are needed to correct these limitations.

When Horstman et al. (11) consider SSU Argus T theoretically compressive, they refer to the tension provided by the SSU to increase continence produced at intra-operatory. It is suggested that this kind of SSU may be used in more severe incontinence. According to these authors, urodynamic study registers increase of maximum urethral closure pressure (what we did not measure in our present study) and flow reduction, but that does not correspond to obstruction at urodynamic evaluation. Still, as mentioned, our patients submitted to SSU Argus T® did not show any flow reduction.

Only detrusor overactivity at post-operatory urodynamic study was significant. It was probably caused by improvement of PPUI, due to resolution of sphincter deficiency, that resulted in a resolution of sphincter deficiency, extinguishing afferent urethral stimulation that would induce to involuntary reflex contraction that caused detrusor overactivity (24).

Urodynamic alterations due to SSU surgeries are not still completely clarified, and probably this is the cause of controversial aspects of the action mechanism of these surgeries. Therefore, future studies should focus on broadening of urodynamic parameters evaluated, with more better measures of urethral function using video-urodynamics, or measurement of urethral pressure, bigger series of patients, and finally, the association with other factors, such as length and position of sphincter unity pre and post-surgical of SSU using Magnetic Nuclear Resonance.

CONCLUSIONS

SSU produced significant alterations of detrusor pressure during maximum flow, and in relation to micturition dysfunction, a significant reduction of detrusor overactivity.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Functional outcomes and quality of life after transobturatory slings: hand – made vs. commercial slings

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ABSTRACT

Surgical correction is the most efficient treatment for stress urinary incontinence (SUI), and transobturator sling (TO) has optimal results. The high cost of commercially available sling kits makes it difficult the access in most Brazilian public health services. Hand-made polypropylene slings, on the other hand, have been previously reported. The aim of the present study was to compare the effectiveness and safety of commercial vs. hand-made polypropylene mesh slings.

Data from 57 women who underwent consecutive TO sling surgery to treat SUI were prospectively collected between 2012 and 2014, and divided in two groups for further comparison. In Group-1, 31 women underwent surgery with commercial slings. In Group-2, 26 women underwent hand-made polypropylene slings. Women were compared according to epidemiological data, perioperative evaluation, quality of life, urodynamic study, cure and complication rates. Results were objectively (stress test with Valsalva maneuver, with at least 200mL vesical repletion) and subjectively evaluated by the Patient Global Impression of Improvement(PGI-I), Visual Analog Scale (VAS) and ICIQ-SF. Success was defined as PGI-I, VAS and negative stress test.

Group-1 (n=31) and Group-2 (n=26) had a mean age of 60 vs. 58years (p=0.386). All demographic data were similar. The mean VLPP was 75.6cmH2O vs. 76.6cmH2O (p=0.88). The mean follow-up was 24.3 vs. 21.5months (p=0.96). Success rates were 74.2% vs. 80.2% (p=0.556), with ICIQ-SF variation of 12.6 vs.15.5 (p=0.139) and PGI-I of 71% vs. 80% (p=0.225). There was only one major complication (urethrovaginal fistula in Group-1). In conclusion, handmade and commercial slings have similar effectiveness and safety. The manufacture technique has important key-points stated in the present manuscript.

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Urinary Incontinence, Stress; Pelvic Floor; Suburethral Slings

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INTRODUCTION

Urinary incontinence is a frequent complaint among women after the fourth decade of life, with an estimated prevalence of 25% in this subset of women in Brazil (1). Stress urinary incontinence (SUI) represents two-thirds of the cases (2), with similar data worldwide (3). It is definitely a major public health issue and affects primarily the quality of life of this female population (4). The association of increased intra-abdominal pressure with dysfunction of urethral occlusion generates the SUI (5). Throughout history, several techniques have been developed. Burch procedure was described in 1961 and was considered the gold standard procedure for stress urinary incontinence. In 1996, Ulmsten et al. demonstrated good results

with the retropubic Tension-free Vaginal Tape (TVT). Currently, the midurethral slings represent the most used worldwide procedures for the surgical treatment of SUI (6). Delorme, in 2001, introduced the transobturator sling (TO) technique, characteristically avoiding a significant urethral tension and not violating the retropubic space (RP). It has similar success rates, with a lower number of complications (7).

There are different types and brands of commercial slings, each of them with its peculiarities and advantages. A major caveat of these commercially available slings is their elevated cost (4). About 70% of the Brazilian population is treated in the public health system. Most hospitals in the public health system do not have access to commercially available slings due to their relatively high prices and no reimbursement of the tape by the public health system. For these women, classical procedures are the only option, as open surgery or autologous fascial slings. Our group has previously demonstrated that autologous slings are a good alternative for mesh slings, even though a slightly higher complication rate can be expected with this technique - noteworthy bladder outlet obstruction (8). For TO slings, a good low-cost alternative that has been previously described is the hand-made polypropylene mesh slings. They seem to have similar results and safety outcomes in previous small series (9, 10). Costs, however, for handmade slings are around 1/10 of commercial counterparts. This huge difference could make accessible this valuable technique in the public health system setting in our country. Currently, hand-made slings are off-label procedures. Even though safety of polypropylene mesh in human procedures have been largely established (11), specifically for vaginal procedures there are legal caveats of a new and not yet established technique. All patients in our series were advised of this limitation and the potential risk of complications (infection, extrusion, obstruction and others) and agreed signing an informed consent form. The objective of the present study was to prospectively compare the efficacy, safety, results and quality of life for women treated for SUI with commercially available vs. handmade polypropylene mesh TO slings.

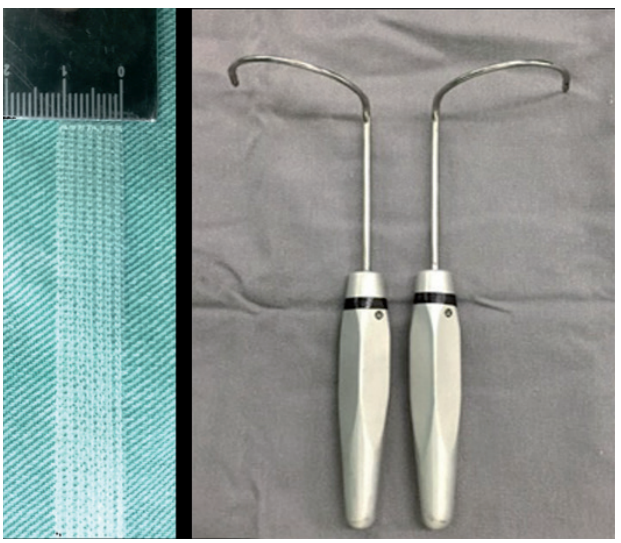
PATIENTS AND METHODS

The present study has evaluated 57 women consecutively treated for predominant SUI with TO slings at the same institution, between January 2012 and December 2014. Exclusion criteria were previous SUI surgery and concomitant surgery for associated pelvic conditions. These women were separated in two groups, according to the type of mesh utilized in each surgery. Commercial meshes were used every time when they were available. Availability of these meshes was possible only when companies donated it for training and demonstration purposes, since it is not a standard product in the Brazilian public health system.

Commercially available slings used were the Obtryx® (Boston Scientific, United States) and Unitape T Plus® (Promedon, Argentina). Hand-made slings were manufactured during each procedure, cutting a polypropylene mesh (Intracorp®-Venkuri, Brazil) to proper size. We have used the same macroporous and monofilament polypropylene mesh in every procedure. Only one sling was obtained from each mesh. To assure reproducibility, all meshes were cut in the lowest elasticity direction, parallel to their lines, counting a total of seven sewing lines wide, resulting in a 1.1cm x 30.5cm mesh (Figure-1). Meshes were cut in a sterile environment in the operating table, immediately prior to surgery, and the remaining mesh was not further used. A permanent transobturator needle was used to pass the sling according to the technique previously described by Delorme et al. (Figure-1) (7). Despite the difference between the meshes, the same surgical technique was performed in both groups. All patients were operated by the same surgeon (LGMT).

Every time there was a commercially sling available, the next patient waiting for surgery received it. When there was no commercial sling available, the next women waiting for surgery was offered the manufactured one as an alternative to other SUI procedures, explaining risks and

Figure 1 - Hand-made polypropylene mesh / Needles.



benefits and treatment. After decision, procedures were conducted when a detailed informed consent form was signed.

All women underwent preoperative clinical evaluation and urodynamic study (in accordance with ICS guidelines). They were evaluated for demographical data (age, height, weight, body mass index, number of pregnancies, vaginal births, caesarean, forceps and abortion, time in years of menopause, hormone use-topical or systemic) and clinical outcomes (type of incontinence, use and number of pads, voiding and storage symptoms, urinary tract infection, dyspareunia, operative time, length of hospital stay, intra and postoperative complications, time with bladder catheter and reoperations). The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) was applied pre and postoperatively (12). Both the Patient Global Impression of Improvement (PGI-I) and Visual Analog Scale (VAS) for treatment satisfaction were applied postoperatively.

A questionnaire was applied pre and postoperatively every three months. The last evaluation of each patient was considered as the definitive results. All surgeries were performed under spinal anesthesia, with antibiotic prophylaxis with cefazolin for 24 hours. All procedures were performed applying the transobturator foramen technique, and manufactured slings were placed with the aid of a permanent needle (7).

Outcomes were obtained through clinical evaluation, questionnaire and stress test, and were divided into objective and subjective success. A stress test was performed with a full bladder and was considered successful when it was negative. When negative, tests were only considered valid if the patient voided at least 200mL after testing. Subjective success was considered when women considered themselves very much better or much better in the PGI-I and scored ≥8 on VAS for satisfaction.

Statistical analysis was performed by skilled professional, using SPSS 13.0v. Student's t test or Mann-Whitney test were used for continuous variables, according to the distribution, parametric/non-parametric. Pearson's Chi-square and Fisher's exact test were used for categorical variables. A significance level α equal to 5% was considered. The present study was approved by the Institutional Review board (CEP-process nº 040686/2015).

RESULTS

Fifty-seven women were evaluated, 31 in Group-1 and 26 in Group-2. Both groups were similar according to demographic and preoperative data (Table-1 and Table-2).

Intra and postoperative data have been reported in Table-3 and Table-4. Operative time and complications were similar between both groups. Length of hospital stay was slightly higher for Group-1 (1.2 vs. 1.0, p=0.009), even though not clinically significant.

Both subjective and objective success rates were similar between both groups according to all scores evaluated (Table-5). Patients with unsuccessful procedures (PGI-I less than 7, in a maximum scale of 10, or failure in the objective test) had similar demographic data, but all of them had preoperatively mixed incontinence, a well-known factor of bad prognosis. A relatively high rate of preoperative dyspareunia was observed (almost one third). De novo dyspareunia after the procedure was 6.4% in the commercial group and 3.8% in the propylene mesh group. Curiously, 4 patients in the commercial group, that even had objective and subjective success, still use a pad in postoperatory, as for insurance.

Table 1 - Demographic data (meanstandard deviation).

	Commercial Sling (n=31)	Hand-made Sling (n=26)	p
Age (years)	60±10	58±10	0.386
Height (cm)	159±7	160±6	0.710
Weight (Kg)	70.3±11.4	73.2±15.6	0.420
BMI	27.8±4.6	28.5±4.9	0.609
Menopause (years)	17.9±10.0	12.3±8.7	0.061
Pregnancy	4.2±2.5	3.3±1.8	0.143
Vaginal Birth	2.6±2.0	1.8±2.2	0.133
Cesarean section	0.8±0.9	1.1±1.3	0.512
Forceps	0.0	0.1±0.3	0.054
Abortion	0.8±1.2	0.3±0.5	0.079

BMI = Body Mass Index

Table 2 – Preoperative urinary symptoms. Data expressed in (mean±standard deviation) or n (%).

	Commercial Sling (n=31)	Hand-made Sling (n=26)	P
Use of Pads	25 (80.6%)	21 (80.8%)	0.991
Number of pads	3.9±2.3	3.4±1.6	0.449
Genuine SUI	5 (16.1%)	10 (38.5%)	0.057
Mixed SUI	26 (83.9%)	16 (61.5%)	0.057
Recurrent UTI	11 (35.5%)	07 (26.9%)	0.489
Dyspareunia	10 (32.3%)	08 (30.8%)	0.904
Urodynamic Study			
VLPP (cmH_2O)	75.8±30.1	76.6±34.7	0.928
VLPP < 60	11 (35.5%)	9 (37.7%)	0.841
Detrusor overactivity	8 (25.8%)	4 (16.7%)	0.412

VLPP = Valsalva Leak Point Pressure; **SUI** = Stress Urinary incontinence; **UTI** = Urinary Tract Infection

Table 3 – Surgical data. Data expressed in (mean±standard deviation) or n (%).

	Commercial Sling (n=31)	Hand-made Sling (n=26)	p
Operative time (min)	33.4±8.4	32.9±8.0	0.731
Lenght of stay(days)	1.2±0.5	1.0±0.1	0.009*
Intraop. Compl.	0	0	-
Postop. Compl.	1 (3.2%)	0 (0%)	1.000
Time with catheter (hours)	30.6±83.5	21.0±3.9	0.563
Reoperation	1 (3.2%)	0 (0%)	1.000

There was only one Clavien-Dindo 3 complication in Group-1, a woman postoperatively diagnosed with urethral injury, requiring reoperation. This patient had a long hospitalization time and remained with an indwelling bladder catheter for 20 days.

Table 4 - Postoperative clinical data. Data expressed in (mean±standard deviation) or n (%).

	Commercial Sling (n=31)	Hand-made Sling (n=26)	p
Follow-up (months)	24.4±15.5	21.5±10.5	0.962
Use of Pads	10 (32.3%)	4 (15.4%)	0.140
Number of pads	1.9±1.2	1.0±0.2	0.097
UTI	3 (9.7%)	4 (15.4%)	0.080
Dyspareunia	5 (16.1%)	1 (3.8%)	0.205

UTI = Urinary Tract Infection

DISCUSSION

Urinary incontinence is a major public health issue. Several surgical techniques have been used historically, but mesh slings have gained worldwide acceptance since it is highly effective, technically easy and with low complication rates. The TO sling technique has high success rates whereas offering low complications rates (7, 13).

Previous studies have demonstrated in a small number of patients that commercial and manufactured polypropylene slings have similar results and complication rates after 90 days, when placed through the retropubic route. Bladder perforations occurred equally in both groups (9). TO technique has also been described with hand-made slings. The low-cost alternative polypropylene mesh slings seem to have similar results and safety in previous small series (9, 10).

Our study has some important findings. First, success rates were similar between both groups, either when considering objective (ranged

Table 5 - Success rates. Data expressed in (meanstandard deviation) or n (%).

	Commercial Sling	Hand-made Sling	p
Objective Success	23 (74.2%)	22 (80.2%)	0.556
Subjective Success	22 (71%)	22 (80.2%)	0.220
ICIQ-SF pre	17.9±3.1	19.8±1.5	0.002*
ICIQ-SF post	5.2±6.1	4.1±5.1	0.645
ICIQ-SF improvement	12.6±7.4	15.6±5.1	0.139
Satisfaction (VAS)	7.7±3.0	9.0±1.1	0.160
PGI-I (scores 1 and 2)	22 (71%)	22 (80.2%)	0.225

ICIQ-SF=International Consultation on Incontinence Questionnaire-Short Form; **VAS**=Visual Analog Scale; **PGI-I**=Patient Global Impression of Improvement

from 72-80%, p=0.0556) and subjective outcomes (71-80%, p=0.220).

Additionally, ICIQ-SF demonstrated similar improvement (Table-5). In a retrospective study, Cifti et al. have demonstrated a success rate ranging from 74% to 80%, similar between both groups in a twelve-months follow-up (10). Cure rates after sling surgery vary in the literature from 70 to 100% and are influenced by several factors such as technique modifications, incontinence severity, parity, surgeon's experience, diversity of patients and subjective criteria, which make it difficult to compare results (6). With polypropylene slings, a 80% efficiency rate in the first five years and 63% after 11 years of follow-up have been demonstrated (13). For TO slings, Sivasglioglu et al. have demonstrated a cure rate of 85% after five years of follow-up (14). These results are similar to what we have found in the present study.

Second, quality of life was similar between both groups. ICIQ-SF domains and satisfaction scale for patients from both groups were similar (Table-5). Even though the similar success rates could predict that satisfaction, we have accessed these results objectively.

Third, complications were similar between both groups. We had a low complication rate in our patients. No intraoperative complications occurred, and there was only one postoperative complication (urethro-vaginal fistula) during the 23 months of follow-up period. This complication occurred in one patient from the commercial sling group after three weeks of follow-up. She was re-operated and the sling was partially removed. In the Turkish study, extrusion occurred in 14.6% of cases in the hand-made group vs. 1.6% of cases in the commercial group (10). In that particular study, authors have cut 15 slings from each polypropylene mesh and re-sterilized it (10). We believe that the technique we have used to manufacture the slings are a strength of the present study. There are dozens of different meshes commercially available, with distinctive characteristics, such as elasticity, pore size, thickness and sewing shape. Thus, the results of the hand-made sling cannot be generalized. The characteristics of the mesh and the variability in sling cutting and implantation can significantly influence success rates and complications. We have used the same macroporous and monofilament polypropylene mesh in every procedure and just one sling was cut from each mesh. Meshes were cut always at the same way, with sterile precaution, in the operating table, and was immediately used. These cautions might be the explanation for the

different complication rates between our study and the Turkish study. Our overall complication rate of 1.7% was similar to reported in larger midurethral slings series (15).

Our study has some limitations. First, due to its retrospective nature, a relatively small number of cases, and a short follow-up period, it cannot bring any definitive conclusion. However, since there is a paucity of studies and our study has demonstrated a different result from the previous ones, it has become very relevant. The present technique allows women from the Brazilian public health system to have access to polypropylene slings in a 10 times less expensive fashion than the commercially available ones.

The length of hospital stay was statistically longer for the commercial group (0.2 days longer), even though this might be due more of a result of bureaucratic issues, and does not pose a clinical relevance. The preoperative ICIQ-SF was higher in the hand-made group, what could suggest that the groups were different. However, this 2-point difference doesn't have a clinical relevance. Moreover, the variation between pre and post-operative ICIQ-SF was similar between groups.

In conclusion, the hand-made polypropylene sling manufactured according to our technique demonstrated to be as efficient and safe as the commercially available kits, with a low complication rate during a two-year follow-up.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Sexual complications of penile frature in men who have sex with men

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ABSTRACT

Objectives: Evaluate the demographic data, etiology, operative findings and results of surgical treatment of penile fracture (PF) in men who have sex with men(MSM) with emphasis on sexual complications.
Materials and Methods: We studied 216 patients underwent surgical correction of PF at our hospital. Patients self-identified as MSM were followed for at least 6 months. Demographic data, presentation, operative findings, International Index of Erection Function - 5 (IIEF-5) and the Premature Ejaculation Diagnostic Tool.
Results: Of 216 PF cases, 4 (1.8%) were MSM. All cases resulted from sexual activity and all patients reported using the "doggy style" position during anal intercourse. Unilateral or bilateral injury of corpus cavernosum was found in 2 patients each. One (25%) patient had complete urethral injury associated with bilateral corpus cavernosum lesion. During the follow-up period, all patients developed some type of sexual complication. One patient reported penile pain during intercourse. Another patient experienced low sexual desire and premature ejaculation. This patient was also dissatisfied with the aesthetic result of the surgical scar and complained about decreased penis size after surgery. The third case developed delayed ejaculation. The fourth patient experienced mild to moderate erectile dysfunction. This same patient presented with penile curvature. Finally, palpable fibrotic nodules in the operative area were observed in all cases.
Conclusions: Sexual activity in the "doggy style" position was the commonest cause of PF in MSM. Sexual dysfunction is always present in gay man after surgery for PF. However, additional studies with larger samples should be coinducted.

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INTRODUCTION

Penile fracture (pf) is an uncommon form of urologic trauma. Sexual intercourse is the commonest cause of fracture of the penis (1). Immediate surgical exploration is the current standard treatment and aims at restoring the anatomical and functional integrity of the penis. However, this approach is not free from complications and sexual dysfunctions can occur (2).

Determining the number of men who have ever had sex with another man (msm) is difficult. In a study conducted in the united states, at least 5% of men, reported having ever had sex with men (3). This population is also at a risk of pf. Nevertheless, most studies on pf have only included heterosexual patients. Moreover, msm have received limited attention in sexual medicine literature and non-heterosexual orientation is an exclusion criterion in many large scale studies in

sexual medicine (4, 5). Moreover, the majority of instruments for the assessment of sexual problems have not been validated in homosexual patients (6). An internet-based survey with men who have sex with men (msm) found that 79% of men reported at least one sexual dysfunction symptom such as low sexual desire, erection problems, and performance anxiety (7). Accordingly, we believe that sexual dysfunction may be present in msm operated on for pf. The aim of this study is to evaluate the demographic data, etiology, operative findings and results of surgical treatment of pf in msm, with emphasis on sexual complications.

MATERIALS AND METHODS

Between january 1997 and december 2016, 216 patients underwent surgical correction of pf at our hospital. Patients self-identified as msm were followed at the andrology outpatient clinic of this institution for at least 6 months.

Epidemiological and clinical presentation data and operative findings were reviewed retrospectively using the medical records. All patients were submitted to the surgical technique utilized in our department, which consists of making a circular sub-coronal incision followed by further penile degloving and reconstruction of the corpus cavernosum and urethra, as necessary (8).

After the sixth postoperative month, patients were interviewed and questioned about any sexual dysfunction. The evaluation of postoperative erectile function was carried out by filling out the international index of erection function - 5 (iief-5) and the premature ejaculation diagnostic tool was used for the screening survey to assess risk of premature ejaculation. Minor modifications to syntax were made and specific terms for the subject's partner were replaced with gender neutral pronouns to adapt it for msm.

The study design was approved by the ethics and human research committee of the institution.

RESULTS

Of 216 pf cases treated in our emergency room between january 1997 and december 2016, 4 (1.8%) were msm. Their age varied from 36 to 46 years old (mean, 41 years) and all patients were single. Time between trauma and surgery varied from 4 to 18 hours (mean, 12.7 hours). All cases resulted from sexual activity and all patients reported using the "doggy style" position during anal intercourse.

With respect to the clinical presentation, all patients experienced immediate penile detumescence. Penile pain and a cracking sound during trauma were noticed by 3 (75%) patients. Extensive penile edema was observed in all cases. Only one (25%) patient experienced urethral bleeding and surgical exploration revealed urethral injury in this patient (Figure-1).

Figure 1 - After a "doggy style" position the patient present penile fracture, we can observe a great hematoma and the typical aspect of eggplant deformity and meatal bleeding. During the surgery we identified a bilateral rupture of the CC and transection of the penile urethra.

All patients were submitted to surgery after clinical diagnosis, without the need for complementary tests. With regard to operative findings, unilateral or bilateral injury of corpus cavernosum was found in 2 patients each. One (25%) patient had complete urethral injury associated with bilateral corpus cavernosum lesion.

Follow-up time varied from 6 to 16 months (mean, 10 months). During the follow-up period, all patients developed some type of sexual complication. It is worth noting that no patient had sexual problems before the trauma. One patient reported penile pain during intercourse. Another patient experienced low sexual desire and premature ejaculation. This patient was also dissatisfied with the aesthetic result of the surgical scar and complained about decreased penis size after surgery. The third case developed delayed ejaculation. The fourth patient experienced mild to moderate erectile dysfunction (iief-5 score = 14) and need oral treatment with phosphodiesterase type 5 inhibitor (pde5) with a satisfactory response. This same patient presented with penile curvature. Intracavernous prostaglandin injection showed a curvature <30°. Penetration was not impaired and the treatment was conservative. Finally, palpable fibrotic nodules in the operative area were observed in all cases (Table-1).

DISCUSSION

There is evidence about the importance of genetic, autoimmune, and neurohormonal factors in the development of sexual orientation. Although homosexuality is widely established as a sexual orientation, the majority of religious authorities, as well as some political institutions, consider sex with people of the same gender unnatural (9).

Table 1 – Demographic data, presentation, operative findings and sexual complications.

Patient	1	2	3	4
Age	36	45	46	37
Etiology	Anal intercourse/ “doggy style” position	Anal intercourse/ “doggy style” position	Anal intercourse/ “doggy style” position	Anal intercourse/ “doggy style” position
Time between trauma and surgery (hours)	18	04	15	14
Presentation	Pain, cracking sound, detumescence and haematoma	Cracking sound detumescence, haematoma and urethral bleeding	Pain, cracking sound, detumescence and haematoma	Pain, detumescence and haematoma
Type of lesion	Unilateral corpus cavernosum	Bilateral corpus cavernosum and urethra	Bilateral corpus cavernosum	Unilateral corpus cavernosum
Sexual complications	Penile pain and fibrotic nodule	Premature ejaculation, low sexual desire, aesthetic dissatisfaction and fibrotic nodule	Delayed ejaculation and fibrotic nodule	Erectile dysfunction, penile curvature and fibrotic nodule

For this reason, many people are still unwilling to report their sexual orientation. Moreover, patients with pf may be too embarrassed to seek medical attention in the emergency room (10). This may explain why we found only 4 cases of pf in msm. In addition, despite our experience with 216 cases since 1997, all patients self-reported as msm only in the last year of this research and, one of these patients reported his sexual orientation at the third follow-up visit when his comfort level with the physicians increased.

Sexual intercourse is often associated with injury, especially if the sex act is more vigorous. Some studies reported that the "woman-on-top" position represented a major risk for pf, as the female partner usually controls the movements, and may inadvertently land the entire weight on the erect penis if it slips out of the vagina (11, 12). The same may occur in msm anal sex. However, it is unknown whether anal intercourse may be associated with an increased risk of pf. Reis et al. Found 4 homosexual patients in his sample of 42 cases of pf. Half of the patients reported being on top and the other half had intercourse in the "doggy style" position (11). In our recent study, we found that pf is most often caused by the "man-on-top" and "doggy style" positions. Moreover, these positions showed more associations with bilateral fractures of the corpus cavernosum and urethral lesions (1). In this study, all cases occurred during sexual activity when anal intercourse was being performed in the "doggy- style" position.

There has been limited investigation of sexuality and sexual dysfunction in non-heterosexual population and much of the medical literature on these sexual minority groups is centered on high-risk sexual behaviors and sexual dysfunction in hiv positive men (13). Despite this, there is evidence in the literature that psychological morbidity tends to be commoner in gays. Moreover, this can be due to secondary societal stigma against homosexuals (14, 15).

Research conducted by Bancroft et al. Evaluated a large sample of homosexual men and matched heterosexual men for erectile dysfunction and ejaculatory problems. Erectile dysfunction is commoner in homosexual men with statistical significance and plays a more critical role in the sexual lives of homosexual men (16). According to Lau, et al., msm who experienced discrimination because of their sexual orientation were more predisposed to erectile dysfunction and premature ejaculation. Those msm who experienced anxiety because of their orientation were more likely to develop performance anxiety and sexual dysfunctions (15). In this study, we observe ejaculatory disturbances, low sexual desire secondary to pf in addition to aesthetic dissatisfaction and we believe they are linked to psychological aspects.

Hirshfield et al. Studied sexual dysfunctions in non-heterosexual men and found lower sexual drive (57%), erectile dysfunction (45%), performance anxiety (44%), lack of pleasure during sex (37%), inability to achieve orgasm (36%), premature ejaculation (34%), and pain during sex (14%). In addition, they noted that sexual problems were reported more frequently by men who were young, not in a relationship, and hiv-positive (7). A belgian study evaluating msm found an incidence of erectile dysfunction of 45% and the most common form of treatment was oral medication (pde5). Most of the msm using such medication (83%) were satisfied with the result of the treatment (17). In our sample, one patient (25%) experienced erectile dysfunction and was treated with pde5 with a satisfactory response.

Reis et al. (11) did not correlate the complications found with sexual orientation, despite mentioning 4 cases of homosexuals operated on for pf in his sample. Thus, we were unable to find studies evaluating the development of sexual dysfunction especially in msm after the treatment of penile fracture. In this study, all patients self--identified as msm had some type of sexual complaint after surgery. These findings are different from those found in other heterosexual patients in our sample. Of 212 pf cases with different etiologies, 53 patients were properly followed up and 24 (45.2%) have developed sexual dysfunctions (ejaculatory dysfunction in 9.4%, low desire in 9.4%, penile curvature in 11.3%, erectile dysfunction in 16% and penile pain in 24.5%).

To our knowledge, the present study was the first to consider outcomes of pf in msm. Nevertheless, this study has limitations owing to the small number of cases and methodological weak-

nesses. The instruments that were modified have not been validated for the assessment of sexuality in this population and may introduce measurement bias. Moreover, we were unable to match heterosexual men with pf during anal intercourse for comparing the complications found in our sample.

CONCLUSIONS

Fracture of the penis is a rare urological emergency and there is a lack of studies with msm. Sexual activity in the "doggy style" position was the commonest cause in this population. Sexual dysfunction is always present in non-heterosexual men after surgery for pf. However, additional studies with larger samples should be conducted.

CONFLICT OF INTEREST

None declared.

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Objective measurements of the penile angulation are significantly different than self-estimated magnitude among patients with penile curvature

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ABSTRACT

Introduction: The study was aimed to assess the presence of actual differences between the objective and the perceived magnitude of a curvature between patients affected by Peyronie's disease (PD) and congenital penile curvature (CPC).
Materials and Methods: Wee analysed a cohort of 88 consecutive patients seeking medical help for either CPC or PD. All patients were invited to provide a self-made drawing of their penis in erection in order to obtain self-provided description of the deformity. An objective measurement of the deformity was also performed drawing two intersecting lines through the center of the distal and proximal straight section of the penile shaft.
Results: Our findings showed significant differences between patient self-estimation and the objective measurements of the penile angulation performed by trained experts, with only 32% of patients correctly assessing their own curvature. Overall, patients tended to overestimate (56%) their degree of curvature, but the results are different in patients with PD than those with CPC. In the 60 men (68%) who did not accurately assess their curvature, PD patients generally overestimated their curvature versus CPC patients (67% vs 16%). On the contrary CPC patients underestimated their curvature compared to PD (42% vs. 4%).
Conclusion: In order to improve patients' satisfaction rates, the surgeon needs to take into consideration the patient's perception of the deformity when planning the type of surgical correction.

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INTRODUCTION

Penile curvature can be classified as congenital (CPC) or acquired. Congenital penile curvature is secondary to an uneven development of the corpora cavernosa and usually becomes evident during adolescence, when the growth of the corporal tissue occurs at its maximum pace. Conversely, Peyronie's disease (PD) is an acquired benign connective tissue disorder involving the tunica albuginea of the corpora cavernosa, leading to the formation of fibrous inelastic plaques (1-4). As the fibrous inelastic plaques do not stretch as the rest of the tunica albuginea, during erections acquired curvature manifests with a variety of deformities including curvature, shortening, narrowing and hinge effect (1, 2).

The natural course of PD is not homogeneous and ranges from spontaneous resolution of all clinical symptoms to severe penile curvature, ED and the complete inability to engage in penetrative sexual intercourse (1, 2, 4).

Surgery remains the mainstay of treatment for patients with CPC and stable PD and the aim of surgical correction is to guarantee a penis straight and rigid enough to allow the patient to resume penetrative sexual intercourse (1, 2). Unless the patient is troubled by refractory erectile dysfunction, the management of CPC is surgical straightening with the use of tunical plications (1). Tunical incision and grafting is almost never indicated in this group of patients as the curvature is harmonic and uniformly spread along the length of the shaft and hinge or hourglass deformities are not present. In patients with PD, the choice of the most suitable surgical intervention should be guided by an algorithm, which takes into consideration the quality of erections, the type and complexity of the curvature, the presence/absence of hourglass deformity and/or distal flaccidity and the degree of penile shortening (1, 2).

Although with an adequate choice of the surgical approach and in expert hands a satisfactory result can be achieved in most cases, patients' satisfaction rates following PD surgery tend to be significantly less encouraging (2, 5). To this regard, the surgical algorithm in PD surgery is based on an objective assessment by the surgeon of the degree of penile deformity (1, 2), but patient self-perception of the deformity can be different. It is in fact well documented that many patients complaining of PD tend to overestimate the degree of their curvature (6). Furthermore, the surgeon is only able to assess the deformity once PD is stable; on the contrary, the surgeon cannot actually appreciate the overall shortening that eventually has occurred. Likewise, usually there is not any morphometric pre-disease assessment which may help to objectively evaluate rates of penile malformations; therefore, the only "picture" of what morphometrically (i.e. shape, length, and curvature) the penis really was before the onset of PD is the one in the memory of the patient.

No previous studies have properly reported the relationship and differences in the perception of penile deformity between patients affected by PD and CPC.

We sought to i) assess the presence of actual differences between the objective (i.e. as assessed by the surgeon after induction of a penile artificial erection) and the perceived magnitude of a curvature among patients affected by PD and CPC; and, ii) correlate patient's self-perception of the degree of penile curvature with objective measures of the same angulation as obtained by trained specialists.

MATERIALS AND METHODS

The analyses were based on a cohort of 88 consecutive Caucasian-European sexually active heterosexual men seeking medical help for either CPC or PD (either in the active or in the stable phase of the disease) between January 2013 and September 2014.

A comprehensive medical and sexual history, physical examination, and targeted laboratory and radiological [Dynamic Doppler Ultrasound (DDU) for patients with PD and penile plaque] investigations were performed in every patient (Table-1). Specific data collected included patient demographics, comorbidities, and regular medications. All patients were invited to complete the International Index of Erectile Function short-form (IIEF-5) (7) and the Beck's Inventory for depression (BDI) (8).

As part of the baseline office assessment, all patients were also invited to provide a self-made drawing of their penis in erection, both from an axial and a sagittal plane, in order to obtain self-provided tridimensional description of the deformity. Likewise, an objective measurement of curvature direction and angle was also performed drawing two intersecting lines through the center of the distal and proximal straight section of the penile shaft. The surgeon recorded both these measurements.

Axial and coronal photographs of the penis during a full pharmacologically induced erection were taken in the office setting by the surgeon during outpatient examination for every patient. In this context, a full erection was defined as the patient's impression of maximal achievable

Table 1 - Characteristics of participants.

	PD n. 69	CPC n. 19
Erectile function		
EF (IIEF<21)	36	9
EF (IIEF>21)	28	6
No intercourse last 3 months	5	4
PDE5i use	22	0
Physical Examination(ICI)		
Curvature <30	9	5
Curvature 30 - 60	29	7
Curvature >60	31	7
Palpable plaque	67	0
PD treatment received		
Vitamine supplementation	26	N/A
Intralesional injection (steroids or verapamil)	14	N/A
ESWL	1	N/A
No treatment	28	N/A
Plaque US		
Isoechoic	18	N/A
Hyperechoic	49	N/A
Calcificated	2	N/A

Vascular parameters recorded with the DDU were within the normal reference range in all patients.

penile rigidity. Patients were initially injected with 10 mcg/mL of PGE1, which was eventually uptitrated to 20 mcg/mL until an adequate erection was eventually achieved.

Using a ruler and starting at the base of the penis (proximal shaft), a straight line was drawn through the absolute center of the straight portion of the penile shaft proximal and distal to the point of maximum curvature. The degree of curvature was determined objectively measuring with a goniometer the angle between the two intersecting lines and recorded in the patient's notes (Figures 1A-D) (9).

Patients who failed to obtain a full erection in this experimental condition were excluded from this study. Similarly, patients who had complex multiplanar curvatures or significant associated deformities (hourglass, indentations) were excluded, as recording precisely the extent of the deformity was not completely reproducible.

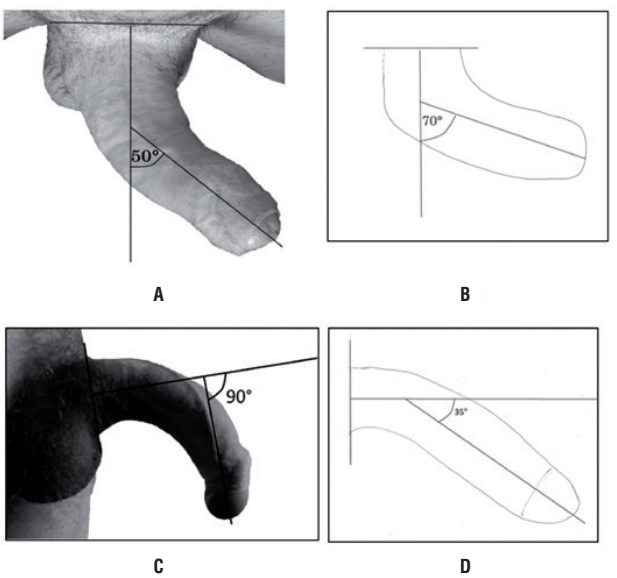
For the specific purpose of the study, patients' perceived curvature and objective measurements were then finally compared; to this regard, patient's assessment was considered accurate if it fell within ± 5 degrees from the objective estimate of the surgeon.

Data collection was done following the principles outlined in the Declaration of Helsinki; all patients signed an informed consent agreeing to deliver their own anonymous information for future studies.

Statistical analyses

Data are presented as median (standard deviation) unless otherwise indicated. Pearson coefficient was performed to evaluate the correlation between the degree of deformity as self-perceived by the patient and the objective measurement. Chi-squared test was applied to evaluate rates be-

Figure 1 - Example of overestimation of the penile curvature in a patient with PD. Objective measurement of the degree of penile curvature was performed on standardized photograph (A) and on the drawing; (B) of the same penis during erection using two intersecting lines. On the other hand, the drawings underestimate the curvature in a case of congenital penile deviation (C, D).



tween groups. A logistic regression analysis tested the correlation between the type/severity of the penile curvature and ED (as defined for IIEF-5 <21), as well as between the degree of curvature and potential curvature overestimation.

Statistical tests were performed using SPSS v.16 (IBM Corp., Armonk, NY, USA). All tests were two-sided, with a significance level set at 0.05.

RESULTS

Table-2 details patient's characteristics as segregated according to the type of curvature. Overall, 69 (78.4%) patients had PD and 19 (21.6%) had CPC. The two groups did not differ in terms of penile curvature degree for physician assessment and IIEF score.

Table-3 lists clinical and disease's characteristics for PD patients.

The results of the comparison between patients' self-perception of the curvature and the objective assessment of the deformity are reported in Figure-2. Of all, 60 (80%) patients did not assess properly their own penile curvature; of them, 49 (81.6%) and 11 (18.4%) patients had PD and CPC, respectively. Within the PD group, 46 (93.9%) patients overestimated their curvature and 3 (6.1%) patients underestimated the curvature. Conversely, 8 (72.7%) patients with CPC underestimated the curvature and only 3 (27.3%) patients overestimated their curvature. Overall, 40 patients assessed properly their curvature, 20 (28%) in the PD group and 8 (42%) in the CPC group.

According to the statistical analysis, the mean patient perceived penile curvature at baseline was 45.97 (SD 19.4) degrees. However, the mean penile angulation obtained by objective measurement was 55.45 (SD 22.2) with a statistically significantly difference from the curvature perceived by the patient ($p<0.05$). The mean curvature at the patient subjective versus surgeon assessment was 59.06 degrees vs 45.43 degrees in the PD group and 42.37 degrees vs 47.89 in CPC group, respectively. The mean difference between the two measurements was: +13.48 (SD 16.2) degrees in PD group and -5.53 (SD 11.5) degrees in CPC group ($p<0.01$).

No differences were founded between PD and CPC by the degree of curvature according to the Kelami classification.

When stratified by the direction, differences between patients' subjective curvature and objective measures were significant for ventral and dorsal curvatures ($p<0.05$), but not for lateral.

Differences between patients perceived curvature and medical therapy were not significant.

Multivariate analysis revealed degrees of curvature ($p=0.018$) and IIEF score less than 21 ($p=0.023$ for IIEF <21) as independents predictors for patient's overestimation.

DISCUSSION

Our findings clearly showed significant differences between patient self-estimation and the objective measurements of the penile angulation performed by trained experts, with only 32% of patients correctly assessing their own curvature. Overall, patients tended to overestimate (56%) their degree of curvature, but the results are different in

Table 2 - Descriptive statistics of the whole cohort of patients [media (SD)].

	PD	CPC	p-value
No. of patients (%)	69 (78.4)	19 (21.6)	NA
Age (yrs)	54 (11.0)	26 (11.7)	<0.001
No. of patients with ventral curvature (%)	1 (1.4)	13 (68.4)	<0.001
No. of patients with lateral curvature (%)	22 (31.9)	5 (26.3)	0.03
No. of patients with dorsal curvature (%)	46 (66.7)	1 (5.3)	<0.001
Penile curvature (degree) Physician assessment	45 (17.8)	45 (24.9)	0.511
Penile curvature (degree) Patient assessment	60 (21.6)	35 (20)	0.002
Δ of measures (degree)	+15	-10	0.006
IIEF score	21 (6.6)	17 (8.3)	0.303
BDI-II score	6 (9.5)	4 (5.5)	0.07

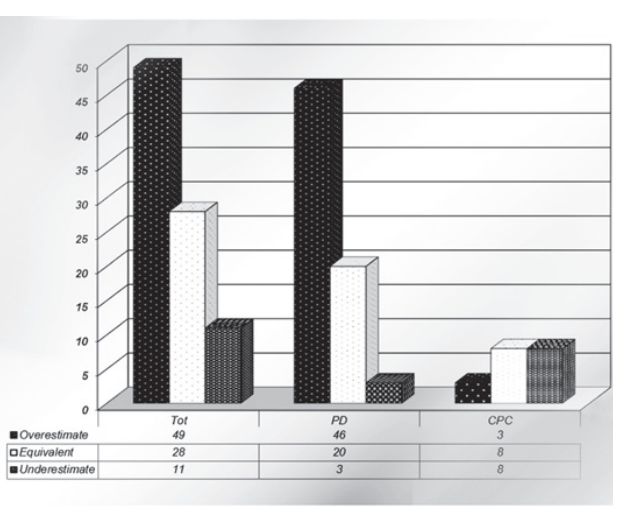
SD=standard deviation; PD=Peyronie's disease; **CPC=**Congenital penile curvature; **IIEF=**International Index of Erectile Function; **BDI=**Beck's Inventory for depression

Table 3 - Clinical characteristics at presentation of patients with PD [No. of patients (%)].

Patients comorbidities		
Hypertension		19 (27)
Diabetes		12 (18)
Dupuytren		11 (16.4)
Stable sexual relationship		55 (80)
Length of the disease, months [median (SD)]		10 (22.3)
First clinical evaluation, months [median (SD)]		4 (10.8)
Pain	Flaccid	8 (12)
	Erection	26 (37)
	Coital	31 (45)
Inability to penetrate		32 (46)
Dyspareunia		18 (25.4)
Anxiety/stress		49 (71.6)

PD = Peyronie's disease; **SD =** standard deviation

Figure 2 - Rates of curvature estimation in the whole cohort, and as segregated for CPC and PD. Overall, most men with PD overestimated their curvature; conversely, men with CPC underestimated or provided a self-assessment of their curvature equivalent to that given by the physician.



patients with acquired curvature than those with congenital curvature. As a matter of fact, in the 60 men (68%) who did not accurately assess their curvature, PD patients generally overestimated than underestimated their curvature versus CPC patients (67% vs. 16%; p<0.005). On the contrary, CPC patients collectively underestimated their curvature compared to PD (42% vs. 4%; p<0.005).

The differences between patient estimates and the actual objective measures emerged to be significant for ventral and dorsal curvatures, but not for the lateral curvatures. At multivariate analysis, both the degree of curvature and the quality of erection, as psychometrically defined with the IIEF-5, emerged as independent predictors of patients' overestimation. Based on the results of our

study, it could be postulated that the direction of curvature also matters: as a matter of fact in our series overestimation occurred in patients with dorsal curvatures. Unfortunately, the overwhelming predominance of the dorsal curvature in the population of PD patients limits this observation.

Strangely, in our series, the IIEF score of men with CPC was lower than PD. Although usually a better erectile function should be expected in men with CPC that are younger than PD, on the other hand, just because they are young and inexperienced and with a genital malformation, CPD patients may have a sexual problem.

Surgical correction of PD involves either shortening the longer aspect of the shaft with a plication-type procedure or lengthening the shorter aspect of the shaft with a relaxing incision followed by grafting. Conversely, penile implants are usually offered to patients with concomitant ED (1, 2).

The aim of corrective surgery in PD is to guarantee adequate axial rigidity and to straighten the penis enough to allow the patient to resume penetrative sexual intercourse (1, 2). As stated, notwithstanding a successful surgical correction can be achieved with an adequate choice of the more tailored surgical approach; patients' satisfaction following PD surgery is not very high (1, 2, 5, 10, 11). For instance, Akin-Olugbade et al. analyzed patients satisfaction rates in a series of 114 patients submitted to penile implants; they reported that men diagnosed with PD had lower satisfaction rates when compared with the general penile implant population, possibly because of the more significant penile shortening experienced by this specific subset of patients (5). These findings have been confirmed by Kueronya et al., who have shown how subjective loss of penile length preoperatively is reported by most patients and that further penile length loss due to surgical correction could lead to a significant bothersome condition, irrespectively of the magnitude of the loss itself (1, 12).

We hypothesized that the reason for the low patients' satisfaction rate could be the different self-perception of the deformity. As a matter of fact, the main limitation of the surgical algorithm for PD is that the choice of the most suitable procedure is based on an objective assessment by the surgeon of the degree of penile deformity, but patient self-perception of the deformity can be different (6). Furthermore, the surgeon is actually able only to assess the deformity produced by PD once the active phase of the disease is over, but cannot appreciate the overall shortening and contracture that has occurred since the onset and throughout the natural evolution of the disease.

To this regard, findings are in contrast with the result of a previous series of Matsushita et al. where only 16% of patients did overestimate the deformity (13). Those findings of Matsushita et al. may be explained by the fact that patients had assessed subjectively their curvature during a spontaneous erection rather than with a pharmacologically induced one. Indeed, a full pharmacologically induced erection would have produced a more significant stretch of the tunica albuginea, when compared with a normal erection, and this would have rendered the deformity more obvious.

Therefore, strength of our findings is the fact that in the present series the deformity has been assessed both by the patient and the surgeon after an intracavernosal injection, in order to minimize potential measurement bias during a spontaneous erection, especially if the rigidity was suboptimal.

Similarly, we decided neither to use self--photography of the erect penis to assess the deformity, nor a vacuum constriction device to obtain an erection because they can significantly underestimate the degree of the curvature, as the quality of the erection produced may be suboptimal (14, 15).

From a clinical standpoint, since men with PD may have poor body image leading to mood disturbances, low self-esteem, and emotional distress, any effort aiming to better understanding patients' expectations should be welcomed (16, 17). This could eventually lead to a different approach to treatment and to the creation of a new surgical algorithm, which will take more into consideration patient perception of the deformity and of the loss of sexual function and may lead to better patients' satisfaction postoperatively.

Moreover, our results seem to show that patients with PD significantly overestimate their curvature than patients with congenital curvature, which, on the contrary, generally underestimate it. Although the reason of this difference is not known and is not the object of this study, we speculated that, if the deformity appears after the patient's self-image has already been well defined, the perception of self-reported magnitude is worse. Otherwise, a patient with a congenital curvature made eye to his penis during the growing and his curvature was self-recognized from their early teens with the development of self-sexual awareness, showing minor psychological implication. Moreover, as opposed to PD patients, it is observed that CPC patients have mainly a ventral curvature and one wonders whether this direction of curvature is exactly the variable of concern. Unfortunately in this group of patients, only 1% presents a dorsal curvature and for this reason a correlation is not viable.

This study is not devoid of limitations that the reader should be aware of and may limit the conclusions drawn from these data. First, this study lacks an appropriate comparison group. It's likely that the limited numbers of congenital penile curvature patients with dorsal curvatures and, similarly, the small number of patient with ventral curvature in the Peyronie's disease patient group, limits any kind of conclusion about whether patients in this population might otherwise overestimate or underestimate their curvatures in this scenario. A second obvious limitation pertaining the fact that our series includes only patients presenting for clinical evaluations, rather than a wider group of patients with PD.

It is likely that patients presenting for clinical management are more distressed about their conditions and are prone to overstate the problem. Lastly, this study did not include the assessment of partners, did not collect data on "risk factors" and was limited in the number of demographic variables assessed. In light of these criticisms and the results of this study, a longitudinal study with a standard baseline and regular assessment is warranted to confirm or contrast the data presented in this manuscript. In addition, future studies that assess the impact on the partner and include an appropriate comparison group would be useful in determining the impact of PD on the patient and the couple.

CONCLUSIONS

Adequate preoperative counselling is extremely helpful to give patients more realistic expectations in terms of surgical outcomes. In this context, because it is well documented that PD may lead to depression, low self-esteem and relationship difficulties, we assessed the potential psychological impact of the disease and depression-related symptoms with self-reported BDI-II (1, 2, 10). To this specific purpose we invited all patients to fill the BID-II in; of clinical relevance, no correlation was observed between the self-assessment of the morphometric alteration of the penile shaft and a potential mood deflection. Conversely, our findings confirmed that, since a complete restoration of what the penis used to look like before the onset of PD is not possible, in order to further improve patients' satisfaction rates, the surgeon needs to take into consideration a patient's perception of the deformity and of the shortening of the penis which is most likely close to the reality during the decision making process and certainly when planning the type of surgical correction (10).

ABBREVIATIONS

CPC = Congenital penile curvature
PD = Peyronie's disease
ED = Erectile dysfunction
DDU = Dynamic Doppler Ultrasound
IIEF-5 = International Index of Erectile Function short-form
BDI = Beck's Inventory for depression

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The history of varicocele: from antiquity to the modern ERA

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ABSTRACT

Men have most likely been affected by varicocele since the assumption of the upright position. In De Medicina, written during the first century AD, Celsus credits the Greeks with the first description of a varicocele, and he recorded his own acute observation: "The veins are swollen and twisted over the testicle, which becomes smaller". Celsus himself is credited with the distinction between varicocele (dilation of surface veins) and "cirsocele" (dilation of deep veins). There has been a long history of treatment attempts and failures, some of which are remarkably strange, that have sometimes culminated in tragedy, as in the case of French professor Jacques-Mathieu Delpech (1772-1832). Although some questions regarding the etiopathology and treatment of varicocele remain unanswered, a succession of more or less conservative attempts involving all medical cultures has been performed throughout history. The report by W.S. Tulloch in 1952 brought varicocele into the era of modern evidence-based medicine, and varicocele surgery finally progressed beyond the aim of merely relieving scrotal pain and swelling. From 1970 to 2000, varicocelectomies gained worldwide attention for the treatment of male infertility. Several innovative procedures to correct varicoceles began to appear in the world's literature as interventional radiology, microsurgery, laparoscopy, and robotics, while comprehensive review articles were also published on the subject of varicocelectomies. Microsurgery is nowadays used worldwide and it can be considered to be the gold standard for correcting infertility linked to varicocele.

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ANTIQUITY

Although men have probably been affected by varicocele since the assumption of the upright position, there is no record of this disease in ancient times. In ancient Egyptian medicine, while hernia and hydrocele are well-described in ancient papyri, there is no mention of varicocele, although it was presumably detected frequently during procedures. Several tomb paintings and reliefs depict servants and workmen with protuberances that resemble scrotal swellings (1, 2).

According to a recent study, an illustrious example of ancient Greek art, the famous Statue A- the Younger (Riace Bronzes, fifth century BC- Reggio Calabria, Italy), was modeled with a reproduction of the left varicocele, which the model was probably suffering from at the time (Figure-1) (3).

The 1st century AD

Varicocele surgery dates back to the first century A.D. According to Hotchkiss, Celsus performed the first documented ligation and cauterization of a varicocele (4). Cornelius Celsus (ca.

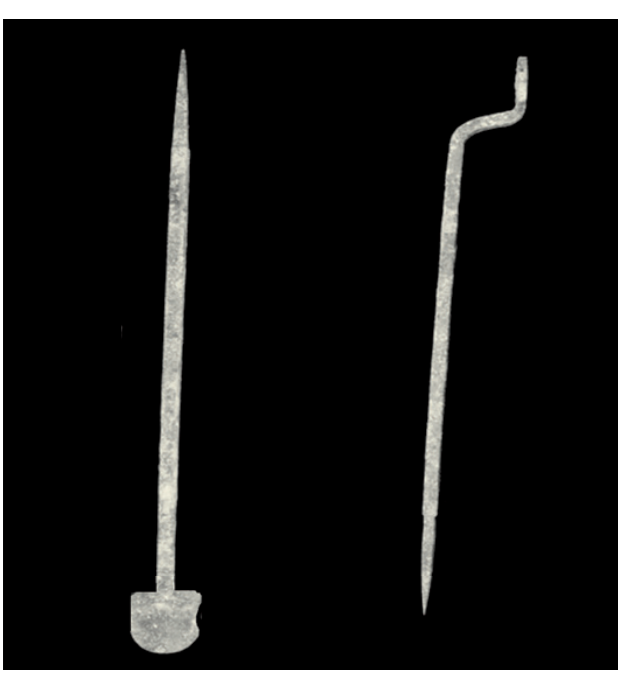
Figure 1 - Riace Bronzes: Statue A, the Younger, and detail of the scrotum.

25BC–ca. 50AD), a Roman nobleman, wrote a general encyclopedia (De Artibus) that covered several subjects, some of which had medical content (De Medicina). It was an eight-volume compendium, including two books on surgery (volumes VII+VIII), and it is the most significant medical document following the Hippocratic writings. Celsus adopted most of the Hippocratic theories and advanced them by presenting a complete description of the etiology, clinical manifestations, and treatments of all diseases and illnesses known at that time. Although largely forgotten for several centuries, Celsus was the first classical medical writer to appear in print (AD 1478) and his writings were highly valued during the Renaissance. Celsus in essence founded the subject of andrology, "ante litteram", as andrological topics are covered in his "De Medicina". In De Medicina, written during the first century AD, Celsus credits the Greeks with the first description of a varicocele, and he recorded his own acute observation: "The veins are swollen and twisted over the testicle, which becomes smaller than its fellow". Celsus himself is credited with being the first to make the distinction between varicocele (dilation of surface veins) and "cirsocele" (dilation of deep veins). Indeed, Celsus warned that the Greek surgeons often confused these two varieties, which they both referred to as "kirsokele";and he added (in De Medicina, VII),"eaeque intortae conglomerataeque venae a superiore parte vel ipsum scrotum implent, vel mediam tunicam, vel imam", referring to internal dilatation of testicular veins.

"De Medicina" acknowledges three levels of intervention: for scrotal varicocele, the surgeon should use the cautery (Figure-2); in more severe cases, ligatures are suggested; and if the varicose vein involves the internal lining of the testicle, then removal of the testis is recommended as it has then become completely useless" (5-8). At that time in history, surgeons used herbal mixtures such as opium, mandrake, henbane, and/or hemlock steeped into a soporific or sleep-bearing sponge ("spongia somnifera"). The sponge was dampened so that anesthetic vapors or drippings could be applied to the patient's nostrils. These sponges were likely historical cousins to the so-called Roman or Arabic sponges (used during crucifixions, surgeries, and other painful events) and the most common sutures were made of horsehair or boar bristles (9, 10).

After Celsus, surgical procedures to treat varicocele were performed only via a scrotal approach.

Figure 2 - Two cauteries from the 1st Century AD. A cautery is a short square-shaped handle with a long, thin or round pointed rod. Roman doctors used cauteries as a counter-irritant, haemostatic, bloodless knife, or as a tool to destroy tumors.



Claudius Galen (130-ca. 200AD) also used the term "cirsocele", although his description of this condition is rather vague despite his copious scientific production (3). Galen performed surgical resection of the surface scrotal veins by lifting them with a hook before isolating and sectioning them (11).

The 7th century AD

After the fall of the Western Roman Empire during the Byzantine period, one of the most authoritative medical scientists was Paul of Aegina (625-690AD). Adhering to an encyclopedic approach to medical writing, Paul composed seven books of comprehensive medical knowledge, "Epitomoe Medicoe LibriSeptem", in which he summarized all of the knowledge available at that time regarding the preservation of health (12).

The sixth book was devoted to surgery. As a highly experienced surgeon, he relied on the prior experiences of Greek and Roman medicine, although he also devised and applied new surgical techniques. In the chapter "On the Excision of Varices", he wrote: "The varix is a dilatation of a vein occurring sometimes in the temples, sometimes in the hypogastric region below the navel, sometimes in the testicles" Paul was the first to recommend a scrotal approach with isolation and protection of the vas deferens before making the incision above the vascular bundle. Unlike Galen, he recommended ligature of the vein distally and proximally, cutting longitudinally and leaving it open to allow the dumping of clots and secretions.

The 10th century AD

Albucasis, from Cordoba (936-1013AD), also recommended a scrotal approach to varicocele, and he left a detailed description of the procedure.

"You must have the patient sitting up in a high chair and take hold of the skin of the testicles with your fingers, together with the blood vessels. Make an oblique incision in the direction of the vessels so that they are laid bare. Then run a double threaded needle through them and tie at the spot where the varix begins. Tie it again where the varix ends, then cut through the varix in the middle and draw out the turbid corrupt humidity that has gathered in it. If all of the vessels are varicose, then you will have to remove one testicle for it will be of no use" (13).

Bruno da Longobucco (ca. 1200 Longobucco-Padua 1286), in his "Chirurgia Magna" (1253) states: "It may happen that the skin of the testicles just relaxes and hangs down so horrendously incise the skin and unite the lips of the wound with a suture". As a result of his extensive knowledge of Greek, Latin, and Arab medicine, Bruno da Longobucco was considered to be one of the greatest surgeons of his time. He was a follower of the surgical practices of Democedes of Crotone, Philistion of Locri, Albucasis, and many others, whose techniques and teaching texts were preserved in Basilian and Benedictine monasteries (14-16). In the centuries that followed, medieval surgery did not contribute much to the treatment of varicocele. Rather, it merely followed the principles outlined by previous authorities.

The 16th century

In 1541, Ambroise Paré gave the most poetic and effective definition of varicocele. He described a condition of "compact groups of vessels filled with melancholic blood and often growing in men of melancholy temper". "Melancholic" probably refers to slow and "toxic" blood and one can therefore assume that Paré was aware of blood stasis in varicocele veins. This concept was to remain constant throughout history, and it was resumed in the early twentieth century in the US by some alternative practitioners (Figure-3).

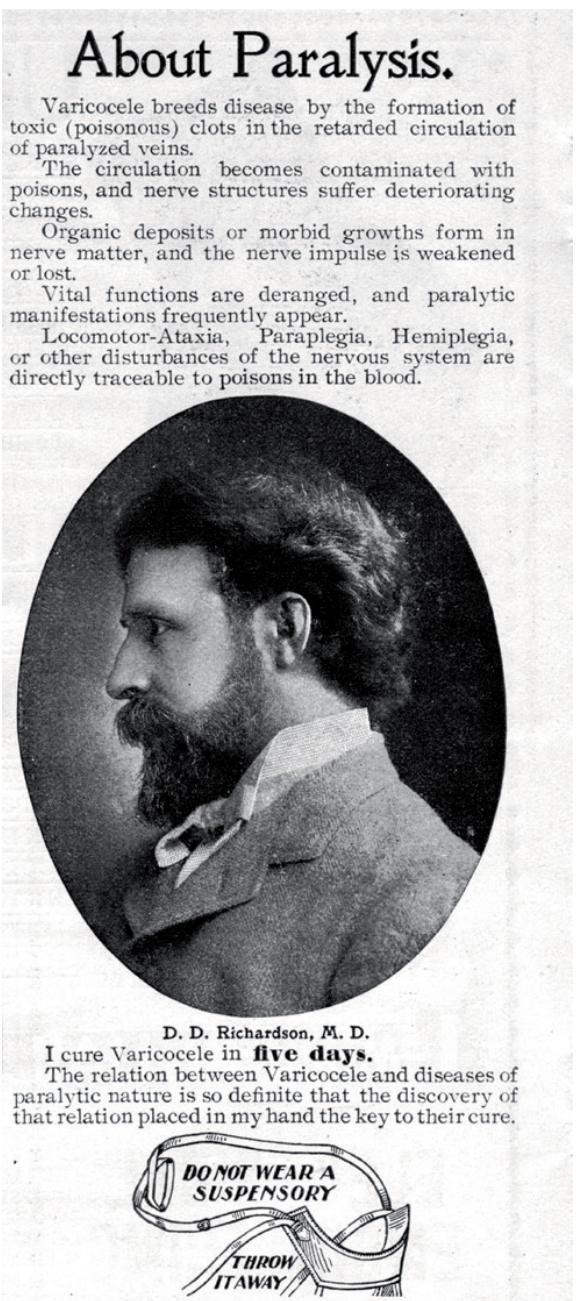
Paré recommended delivery of the dilated veins through a 2-inch scrotal incision with subsequent use of a double ligature instead of cautery (17).

The great French surgeon and anatomist Pierre Dionis (1643-1718) had a more conservative attitude.

"If there is a varicocele (considered as a dilation of the surface veins of the scrotum), it is necessary to start by prescribing numerous bleeds to drain the vessels, and to impose a correct lifestyle to prevent the vessels from filling up again; then apply to the swollen part a large compress soaked in astringent wine and cover it with a suspensor to support and compress the areas to facilitate the correct outflow of the blood. In ancient

times these veins were cauterized in several places with pointed and rounded cauteries, but this excessively harsh procedure is no longer used today. Nowadays, these veins tend to be opened with an S-shaped scalpel when general remedies like astringent wine and the suspensor fail to offer the patient relief.

Figure 3 - An advertisement in the Chicago Tribune in 1899 heralding the virtues of a varicocele cure in five days. The advertisement states "Do not wear a suspensory. Throw it away".


About Paralysis.

Varicocele breeds disease by the formation of toxic (poisonous) clots in the retarded circulation of paralyzed veins.

The circulation becomes contaminated with poisons, and nerve structures suffer deteriorating changes.

Organic deposits or morbid growths form in nerve matter, and the nerve impulse is weakened or lost.

Vital functions are deranged, and paralytic manifestations frequently appear.

Locomotor-Ataxia, Paraplegia, Hemiplegia, or other disturbances of the nervous system are directly traceable to poisons in the blood.

D. D. Richardson, M. D.

I cure Varicocele in **five days.**

The relation between Varicocele and diseases of paralytic nature is so definite that the discovery of that relation placed in my hand the key to their cure.

DO NOT WEAR A SUSPENSORY

THROW IT AWAY

The wisdom of discarding suspensories and

The surgeon opens the veins in the areas that are more dilated, draining out all the blood, using astringent wine and the suspensor. This technique will enable healing, ensuring that the new blood can continue to circulate.

If there is a cirsocele (considered to be the veins inside the scrotum), all authors agree that there is only one form of treatment, this being amputation of the testicle: I personally find that the remedy is worse that the ailment, and I have never used this technique.

I recommend bleeding from time to time, a restrictive diet, abstinence from strenuous exercise, and the constant use of a suspensor to provide relief from pain when the testicle is not supported; and unless obligated by severe need, treatment of this disease should not be undertaken at the expense of the testicle" (18, 19).

The 18th century

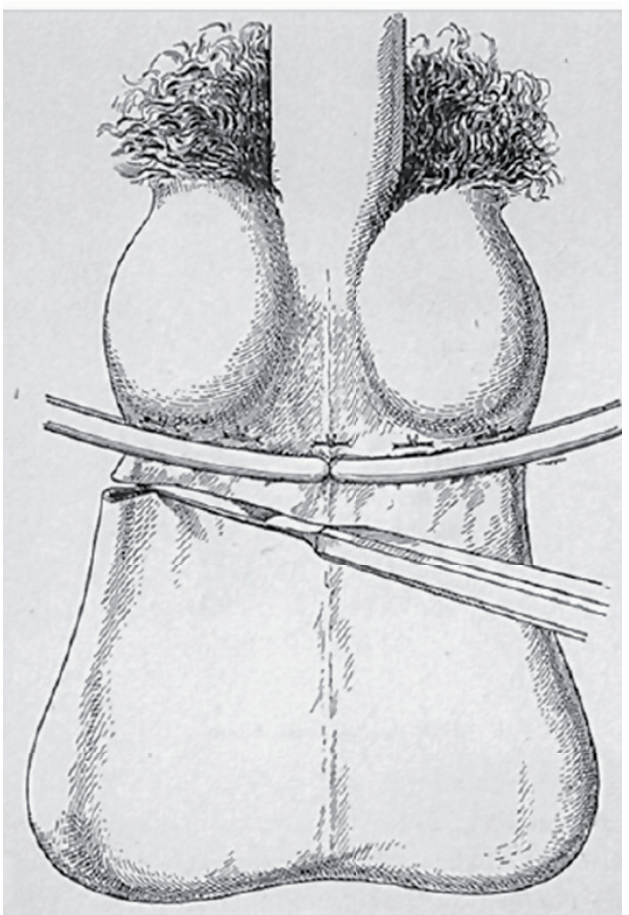
Sir Astley Paston Cooper, 1st Baronet (1768-1841), was an English surgeon and anatomist who made historical contributions to otology, vascular surgery, the anatomy and pathology of the mammary glands and testicles, and the pathology and surgery of hernia. Astley Cooper, a student of the eminent John Hunter, became the most acclaimed surgeon of his time. He provided a very personal interpretation of varicocele as "orchidoptosis", consisting of a plastic reduction of the scrotal sac (Figure-3).There is a famous story told by Cooper about one of his patients, an experienced rider, who after undergoing this procedure traveled 50 miles on horseback without any pain (20, 21).

From then on, a wide range of devices for scrotal section was developed: Heurteloup, King, and the Lewis scrotal clamps (Figures 4-6). At the beginning of the 19th century, the most common form of intervention was a double-thread ligature (silver, lead) of the entangled veins at the base of the scrotum, sparing the deferent and the deferential artery. Special needles were used for the passage (22).

One of the earliest surgical procedures was that of Vidal de Cassis. This method consisted of passing an iron pin through the scrotum between

the vas deferens and the enlarged veins. A silver wire was then passed along the pin outside the veins, which were included between the pin and the wire. The wire was then fastened to the ends

Figure 4 - Cooper's reduction scrotoplasty: partial excision of the scrotum, leading to an upward adjustment of the affected testicle ("inner support").



of the pin, and the pin was twisted to exert a certain amount of pressure on the vessels. The twisting process was repeated every day or every other day until the veins ulcerated and the pin became loose; both the pin and the wire were then withdrawn. The veins were sectioned and inflammatory adhesions were eliminated (Figure-7) (23).

The technique involving ligature at the base of the scrotum was also used by the French surgeon Jacques Mathieu Delpech (Toulouse 1772-Montpellier 1832), who, in some cases, alternated it with a type of sclerotizing treatment:

Figure 5 - King's (upper) and Andrew's (lower) scrotal clamp. Reduction scrotoplasty, unlike that of Cooper, involved the application of the clamps longitudinally following the median raphe. Andrew's clamp was specifically designed to obviate injurious pressure on the tissue during the operation.

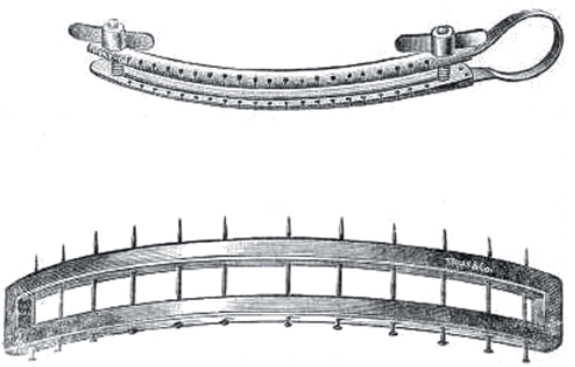
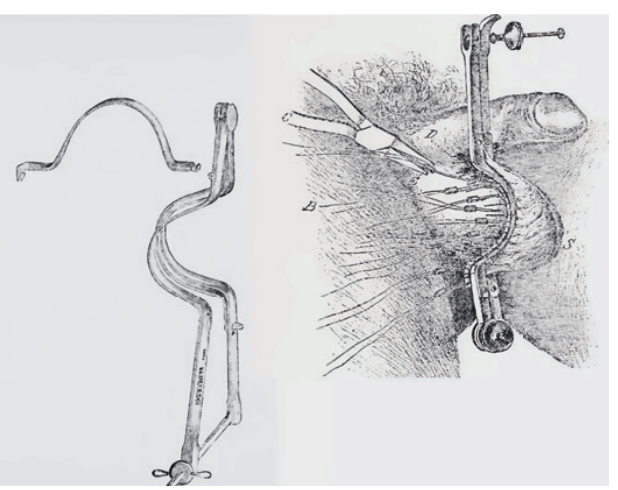


Figure 6 - Heurteloup's scrotal clamp. It was an effective cutting device to isolate and cut the redundant scrotum. After having detached the removable blades, transfixed wires blocked with lead beads were applied.



after longitudinally cutting into the scrotum and exposing the venous plexus, he applied a coating of Touchwood mushroom (a cauterizing agent for wounds, already described by Hippocrates in the 5thcentury BC), which was removed after four days (24) (Figure-8).

The simultaneous treatment of a bilateral varicocele, which was a remarkable feat for that time, resulted in the death of the great French surgeon, who was murdered by one of his patients, Marc Demptos, who he was said to have operated on unsuccessfully a year earlier for bilateral vari-

coceles. The story was in fact considerably more complex than that. Delpech was murdered because he was accused of having betrayed professional secrecy. On Sunday, October 28th, 1832, during an evening at the theatre with his son, Delpech was approached by Demptos, who asked the Professor to retract the news given to the mother of his wealthy fiancée about his infertility as a result of the operation. They had a very heated discussion and Demptos left the theatre highly enraged. On Monday, October 29th, Delpech left Saint-Éloi Hospital (presently the Rectorate of Montpellier) for the Institute of Orthomorphia (modern-day Orthopedics). He was accompanied by his valet who drove the carriage. As the carriage reached the road to Toulouse, Demptos came out of a house holding a double-barrel rifle. He shot twice, killing Delpech and his valet on the spot, after which he returned to his room and shot himself.

Figure 7 - Vidal's technique: with the patient standing upright, the vas deferens were isolated and two silver wires, one large and the other one small (i.e. one thicker, the other one thinner), were passed behind and in front of varicose veins. The two wires were then progressively rolled until the veins ulcerated.

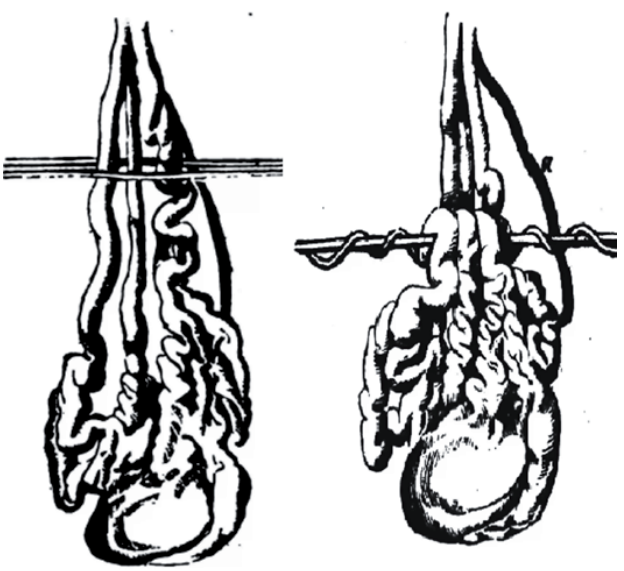
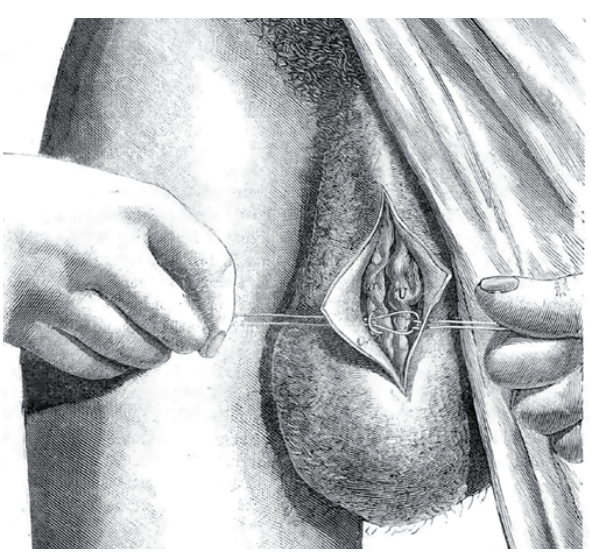


Figure 8 - One of the most popular techniques for varicocele ligation in the 19th century (scrotal window) involved ligature of the varicose packet with two loops, anterior and posterior, passed with a transfixed needle, thereby saving the vas deferens.



The autopsy revealed the murderer's testes to be soft and shrunken, presumably from the operation (25, 26).

For centuries, varicocele was treated solely in order to relieve the dragging weight and pain. The 19th century literature is full of various treatment methods recommended for pain relief, for when the testicle was atrophic, or in case the sufferer had been disqualified from public service. In the mid-19th century (1856), Thomas Blizard Curling (London 1811-1888), observed "a decrease in the secreting powers of the gland" and suggested, for the first time, a relationship between varicocele and male infertility. Curling's name is also linked to the definitive adoption of the term varicocele rather than cirsocele, which was originally coined in 1843 to describe the pathologic dilatation of veins of the spermatic cord and the procedure for diagnosing varicocele by reducing the swelling with the patient in a supine position and then palpation in an upright position (27).

The 19th century

The end of the 19th century was a time of "radical cures" for many common surgical diseases. Eduardo Bassini's "radical operation of the inguinal hernia" was developed and perfected in 1883-1887. In 1890, Bassini published successful results in regard to 262 hernia repairs. This new technique not only changed the

approach to hernia repair, but also to inguinal surgery in general. Bassini's contribution was to focus on the rear wall as the real repair site by approximating the internal oblique muscle, the transversus abdominis muscle, and the transversalis fascia with the iliopubic tract and the shelving edge of the inguinal ligament (28).

Dr. Albert Narath (1864-1924), a professor of surgery in Utrecht and then in Heidelberg (1906-1910), had broad surgical interests, including the treatment of varicocele. In 1900, he described the first truly inguinal approach to dilated spermatic veins. The idea of using Bassini's procedure "to section the main trunk of the vena spermatica interna in the inguinal canal" came from the recognition of "venectasia" within the inguinal canal during hernia repair. Narath first performed this procedure in 1898. Two years later, Narath concluded that "these inguinal incisions are undoubtedly preferable to the old scrotal incisions". This operation was the first to shift the focus from the scrotum to the inguinal area (29).

The 20th century

After these events, varicocele surgery was shaped largely by developments in Central and South America. In his report in 2014, Gonzalez laid the foundation for a proper designation of surgical procedures that, by eponyms, are identified using the names of these surgeons (30). This distinction plays a very important role because, at present, these procedures are still among the most popular surgical techniques for this condition. In 1918, Dr. Oscar Ivanissevich, working in Buenos Aires, described the anatomy of the spermatic vein, and he proposed a supra-inguinal approach to spermatic vein ligation. The rationale for this approach was to ligate the vein where it was most likely to have a single trunk. In 1960, he reported his experience with more than 4.000 cases using the supra-inguinal approach and he provided detailed illustrations regarding his technique. Bernardi, a disciple of Ivanissevich, advocated a transinguinal approach to spermatic vein ligation. In his 1960 article, however, Ivanissevich is critical of Bernardi's transinguinal approach, stating that this approach is more likely to encounter multiple venous trunks and risk missing veins. In 1949, Palomo described a procedure that involved the ligation of artery and vein, without the risk of testicular atrophy, in the retroperitoneal space. This is the procedure that is used nowadays, both in open and laparoscopic surgeries.

Doctor Alejandro Palomo was a urologist who was born in Guatemala in 1917. He graduated from the San Carlos University Medical School of Guatemala in 1942. He trained in Urology at New York Hospital, under Dr. Oswald Lowsley, from 1943 to 1945, and subsequently returned to Guatemala. In Guatemala, he was Professor of Urology at San Carlos Medical School and he served as Chief Urologist at Guatemala City Hospital, where he developed his technique for the treatment of varicocele. In a 1947 publication entitled "Radical cure for varicocele. Modification of Doctor Ricardo Bernardi's technique", he described ligation of both spermatic arteries and veins at the internal inguinal ring. The classical report was then published in 1949 as "Radical Cure of a Varicocele by a New Technique" (31). Based on a study of a small group of 40 men, he noted that three arteries supplied the testis. He concluded that, as long as only two arteries were ligated, the flow from the remaining artery would supply sufficient blood to the testis.

The procedure was carried out under local anesthesia. The incision for this procedure was 4cm in length and 3cm above the internal ring. The dissection was just above the internal inguinal ring, where the large spermatic veins are readily visible. Although the artery and veins were ligated together, Palomo excluded the deferential and cremasteric arteries, which he believed supplied sufficient blood to the testis. Among his first 40 cases, there were no relapses or evidence of atrophy, although hydrocele formation was not discussed.

Some authors have mistakenly applied the term "modified Palomo" procedure to the retroperitoneal approach preserving the artery, as it is in fact the Ivanissevich procedure (32-35).

The first studies to document an improvement in semen quality and an increase in

pregnancy rates following treatment of varicocele were by Barwell in 1885, Bennett in 1889, and Macomber and Sanders in 1929 (36-38).

William Selby Tulloch (1913-1988) was the first surgeon to repair a varicocele for the treatment of infertility. His initial report described an infertile man with bilateral varicoceles and testicular biopsy-proven maturation arrest. This patient was able to attain an increase in sperm concentration and give rise to a natural pregnancy after their varicocele was repaired. Tulloch used the Robb procedure, which approached the spermatic veins 5 cm above the internal inguinal ring. At this site, he felt the dilated veins were fewer in number and the arterial blood supply to the testis could be avoided (39, 40).

Tulloch's report contributed to the worldwide acceptance of the role of varicocele in male infertility. With these new aims, varicocele surgery entered the modern age, making use of the increasingly sophisticated technologies that were becoming available.

This brings us to the field of operative radiology, the use of the operating microscope, laparoscope, and robot-assisted laparoscopy.

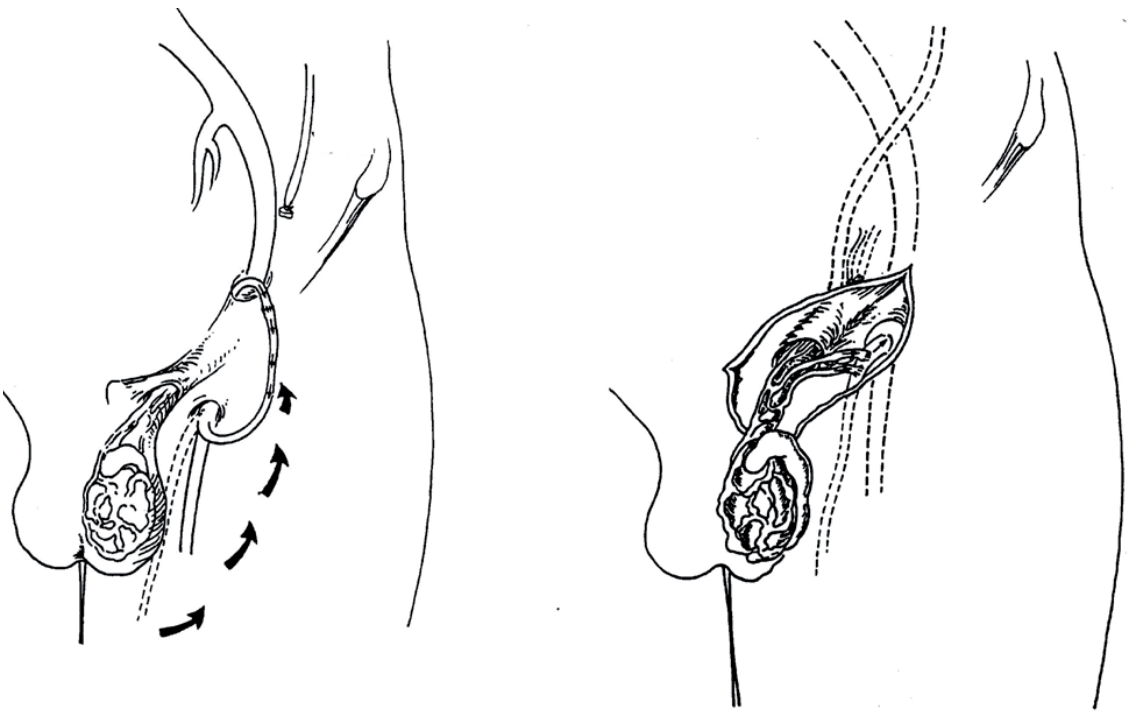
In 1976 Comhaire and Kunnen (41) demonstrated that when contrast medium is injected during selective retrograde catheterization of the left internal spermatic vein at its orifice in the renal vein, patients with varicocele, standing in the erect position, present a retrograde filling of the varicose spermatic vein. Later, in 1978, Lima et al. induced the sclerosis of refluxing veins by catheterization of the internal spermatic veins with the injection of a 75% hypertonic glucose solution (42). The injection was repeated several times until the caliber of the vein was significantly reduced. In light of these results, other substances and devices have been tested, such as 2-isobutyl-cyano acrylate, steel coils, and detachable balloons (43). Although the development of sclerosing techniques were originated in the 20st century, the development continued into the 21st century. Further progress towards achieving effective and minimally invasive treatment of vein reflux was made by Tauber, who introduced sclerotization via direct injection of a sclerotizing substance through a cannula into a refluxing vein. The procedure could be carried out on an outpatient basis and under local anesthetic through a small incision at the root of the hemiscrotum, distal ligation (to avoid accidental injection toward the testis), and injection of 3mL of sodium morrhuate with the "air block technique" (44). The technique was then described in detail in the "Surgery Illustrated" published by the British Journal of Urology in 2006, presenting a case history of over 6.000 patients and using the less toxic polidocanol at 3% instead of sodium morrhuate (45).

The advent of the operating microscope and the affirmation of microsurgery marked another important step forward in the treatment of varicocele. In fact, the operating microscope was first used at the beginning of the 1970's, with various forms of vascular microanastomosis techniques, with the intention not to completely close the refluent veins, but to create venous outflux into another vascular area. Ishigami was the first to propose terminal-terminal microanastomosis between the spermatic vein and the saphenous vein (Figure-9). This operation presented certain negative elements in that, aside from requiring two incisions, one on the thigh and one at inguinal level, it created a risk of stenosis or thrombosis of the anastomosis due to the long subcutaneous tunnel required by the transposition of the saphenous vein (46).

Further microanastomosis techniques followed: terminal-lateral between the spermatic and saphenous veins, and between the spermatic vein and the distal portion of the lower epigastric vein (47, 48). However, microsurgical diversions proved to be too complex for routine usage (49). In addition, there were other complications related to varicocele surgery such as injuries to the testicular arteries (50) and disruption of the lymphatics that produced post op hydroceles (51).

In 1985, Marmar et al. (52) proposed a combined microdissection of the spermatic cord at the external inguinal ring, ligation of the dilated veins, and controlled sclerosis of small cross-collateral veins. The procedure was performed with an operating microscope and mi-

Figure 9 - Microsurgical anastomoses. (Left) Ishigami's technique: testicular-saphenous anastomosis. (Right) The Fox technique: direct anastomosis of two or three dilated veins of the pampiniform plexus with the great saphenous vein.

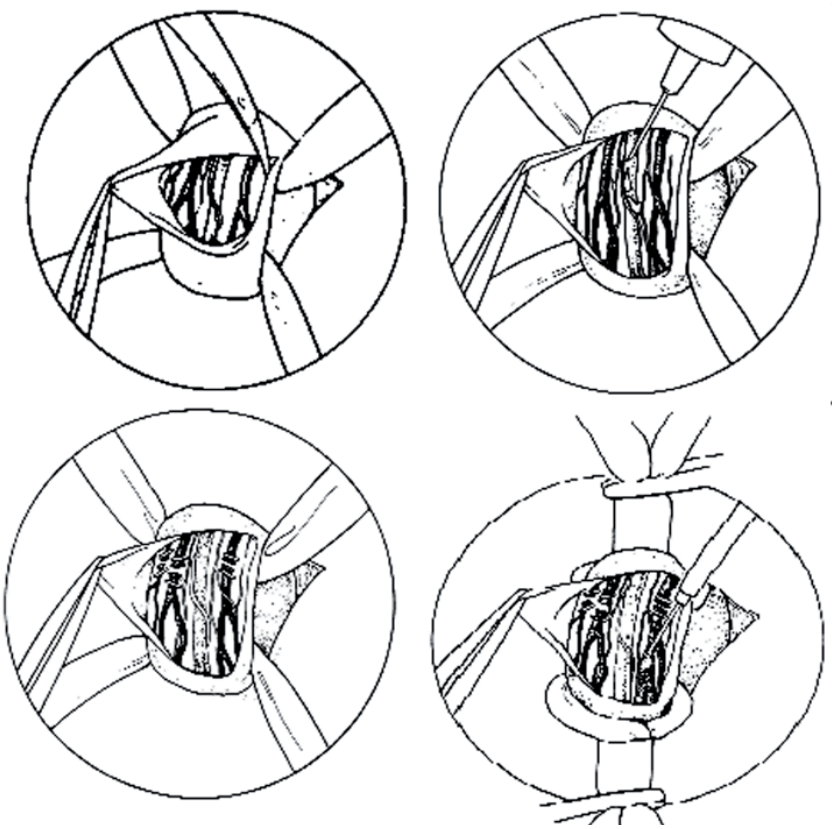


crosurgical instruments. Among 71 cases, there were no post hydroceles and 2 palpable recurrences (0.28%). In this initial report, the semen parameters demonstrated statistically significant improvement and the pregnancy rate was 29.9%. However, in 1994, Marmar and Kim reviewed their experience with 466 subinguinal microsurgical varicocelectomies. There was only 1 permanent hydrocele, a palpable recurrence rate of 0.82% and a 1yr pregnancy rate of 35.6% (53) (Figure-10).

In 1992, Goldstein modified the microsurgical, subinguinal varicocelectomy, taking a more aggressive approach with arterial and lymphatic microsurgical dissection and venous ligation by an arterial and lymphatic sparing technique that in most procedures involved delivery of the testis (54). The authors reported a failure rate of 0.6% for all of the procedures, and a pregnancy rate per couple of 43% within 6 months (Figure-11). In time, other investigators questioned the need to deliver the testicle as part of a microsurgical inguinal varicocelectomy, for example Ramasamy and Schlegel (55) in their comparative study, demonstrated that there were no varicocele recurrences with either procedure, and that delivery of the testis did not offer any beneficial effects on semen quality or pregnancy rates after varicocelectomy. Microsurgery is nowadays used worldwide and it can be considered to be the gold standard for correcting infertility linked to varicocele.

Cayal et al. encountered significant differences among the techniques as they found overall natural pregnancy rates of 37.69% for the Palomo technique series, 41.97% for microsurgical varicocelectomy techniques, 30.07% for the laparoscopic varicocelectomy techniques, 33.2% for radiologic embolization, and 36% for the macroscopic inguinal (Ivanissevich) varicocelectomy series (p=0.001) (56, 57). The authors concluded that open microsurgical or subinguinal varicocelectomy techniques have been shown to result in higher pregnancy rates, fewer recurrences and postoperative complications than conventional varicocelec-

Figure 10 - Marmar's subinguinal microsurgical technique. Delivery of the testis is not performed; the varicose veins are clipped with hemoclips and transected, with controlled sclerosis of small cross-collateral veins. Proximal and distal control of the spermatic cord is obtained by cinching the Penrose drains.

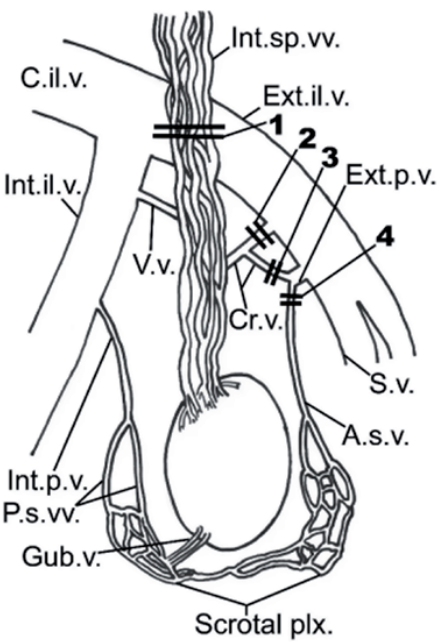


tomy techniques in infertile men. Use of higher magnification allows surgeons to preserve the testicular arteries and lymphatics and also to visualize and occlude all spermatic veins. However, further prospective randomized trials are needed to directly compare with other treatment modalities in infertile men with varicoceles. A more recent report by Shulster et al. regarding simultaneous treatment of varicocele and inguinal hernia showed that microsurgical techniques can also minimize the complications of inguinal hernia repair, such as vasal obstruction, testicular atrophy, recurrence, infection, hematoma, chronic postoperative pain, and loss of sensation (58).

In the mid-1980s, the introduction of laparoscopic cholecystectomy represented a historical turning point that was as momentous as the discovery of anesthesia, asepsis, antibiotics, extracorporeal circulation, and the use of operating microscopes (59). In 1991, Aaberg reported the first experiences of Palomo performed using laparoscopy (60). In 1992, Hagood et al. and Donovan et al. (61, 62) reported laparoscopic varicocelectomies with sparing of the spermatic artery. They reported that a laparoscopic camera provided a good level of magnification of vascular structures. The arteries could readily be visualized after a papaverine drip, and the internal spermatic veins were identified and clipped without difficulty. Donovan reported a mean operating time of 101/153 minutes.

The principle of laparoscopic varicocele ligation is based on the following steps: peritoneal approach; opening a small window on the posterior peritoneum at a distance of 1-2cm from the inner inguinal ring; isolation of the vessels and their ligation or sealing "en bloc" or exclusion of the artery and the lymphatics. The procedure is facilitated by the magnifying

Figure 11 - Goldstein's subinguinal microsurgical technique. This technique involves a more aggressive approach with arterial dissection and venous ligation, and delivery of the testis as part of the procedure to ligate gubernacular veins.



effect of the laparoscopic lens, which allows for excellent visualization of the structures of the vascular bundle.

To achieve better visualization of the lymphatics, recent findings have shown that the intra-dartos/intra-testicular injection of isosulfan blue is significantly better than the previously described intra-dartos injection, thereby allowing for identification of lymphatic vessels in 100% of the cases in our series (63).

The 21st century

With the increase in familiarity regarding the use of laparoscopy and technical progress through the introduction of curved instruments, the procedure was recently also carried out with SILS (Single Incision Laparoscopic Surgery). In 2008, Kaouk et al. reported their initial experience in children using a multichannel single laparoscopic port inserted in the umbilicus. The testicular vessels were then dissected from the lymphatics, and the vessels -both artery and veins- were transected leaving clips both proximally and distally (64). In 2014, Marte et al. have reported their experience with SILS laparoscopic Palomo varicocelectomy in adolescents compared to the traditional procedure. The results revealed no significant difference in terms of the operating time and the incidence of secondary hydrocele, although the postoperative pain score was significantly better with SILS (65). Another minimally invasive approach is represented by retroperitoneal varicocelectomy. This technique uses one 12mm trocar with a short, 27cm, 0 operative telescope and a 5.5 operating channel. An incision is made right below the 12th rib at the posterior axillary line. A muscle- splitting dissection is performed to gain access to the retroperitoneal space. The port is installed and CO2 insufflation is initiated to create the working space, which is progressively enlarged by moving the type of telescope. Once the retroperitoneal working space is created, the spermatic vessels are identified at the site where they cross the ureter. The testicular artery and one or two veins are dissected from the peritoneum and then coagulated by monopolar or bipolar electrocautery (66).

This brings us to the present day situation and the affirmation of robot-assisted surgery has led to the first published reports of robot-assisted varicocelectomy in both adult and pediatric patients. Corcione et al. were the first to use a robot-assisted da Vinci® platform in association with a laparoscopic varicocelectomy (67). Shu et al. performed the first eight robot-assisted subinguinal varicocelectomies and they compared the data relative to eight patients who had conventional microsurgical procedures. The operating times were the same and neither group experienced complications (68). Hidalgo et al. reported their experience with robot-assisted left-side varicocelectomy in four pediatric patients with a mean age of 15.3 years. The authors reported no significant difference in operative time (p=0.02) and no intraoperative or postoperative complications, although the costs for the robot-assisted group were significantly higher (i.e. $15.800 vs. $8.600, p=0.0005) (69).

In conclusion, it is safe to say that treatment of varicocele has entered the age of modern evidence-based medicine, and that varicocele surgery has finally progressed beyond merely providing relief of scrotal pain and swelling. There is now convincing evidence that varicocele may have a progressive harmful effect on the testes, resulting in a decline in semen parameters. Recent studies on the pathophysiology of varicocele-related infertility have revealed the likely influence of ultrastructural testicular changes and increased oxidative stress, with implications for the seminal antioxidant capacity and sperm chromatin integrity (70). The methods used to correct varicoceles started from crude beginnings. However, in recent years, there have been innovative advances in surgical techniques to correct these lesions. In addition, there has been striking developments of biomolecular and functional sperm tests (71, 72) to evaluate infertile men with varicoceles. Therefore, going forward, it should be possible to better understand the mechanism leading to infertility caused by varicoceles, and the techniques reported in this text will offer effective ways to reverse the problems.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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^{99m}Tc-DTPA Diuretic Renography with 3 hours late output fraction in the evaluation of hydronephrosis in children

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ABSTRACT

Objective: Dynamic renal scintigraphy complemented by late gravity assisted postvoid images to 60 minutes is a frequently used diagnostic test in the evaluation of hydronephrosis. The objective of this study is to evaluate the effectiveness in acquiring images at 180 minutes to calculate the late output fraction (LOF) of ^{99m}Tc-DTPA in the diagnosis of ureteropelvic junction obstruction (UPJO).

Materials and Methods: A retrospective study of 177 patients (196 renal units) of suspected cases of clinical UPJO was conducted. The patients were submitted to at least two dynamic renal scintigraphies of ^{99m}Tc-DTPA, with the addition of furosemide (F0), with a mean age of 4.3±3.8 years for the first study, and a follow-up of 2.7±2.5 years.

Results: For diagnosis based on renal curves, a 100% sensitivity, 82.2% specificity, positive predictive value (PPV) of 10.4% and negative predictive value (NPV) of 100% were estimated. For diagnosis based on LOF, a 100% sensitivity, 96.3% specificity, PPV of 35.7% and NPV of 100% were estimated.

Conclusion: A LOF <10% is indicative of UPJO, and a LOF ≥15% is indicative of no UPJO. The data demonstrate that LOF presents equivalent sensitivity and NPV, and higher specificity and PPV in comparison to diagnosis based on renal curves, and is useful in the evaluation and follow-up of suspected cases of UPJO.

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INTRODUCTION

The routine use of fetal ultrasound (US) is an important resource in the early detection and treatment of hydronephrosis caused by ureteropelvic junction obstruction (UPJO). The incidence of hydronephrosis in fetal and neonatal ultrasound is on the order of 1 to 5% and may be caused by various conditions such as vesico-ureteral reflux, obstructions to the urinary ducts and transitory dilation of the renal calyces, pelvis or ureters (1). The challenge created by the detection of antenatal hydronephrosis (ANH) is the correct identification of effectively obstructed cases (10 to 30%), as opposed to transitory hydronephrosis cases (41 to 88%), where surgery should be avoided (1).

The evaluation of patients with ANH in general is based upon pelvic dimensions determined through ultrasound, complemented by micturating cystourethrogram and renal function evaluation through renal scintigraphies dynamic (DYN) with ^{99m}Tc-DTPA or ^{99m}Tc-MAG3 and static with ^{99m}Tc-DMSA.

Although the analysis of the renogram is the most usual in the evaluation of the capacity to eliminate radiopharmaceuticals filtered by the

kidneys, especially $T_{1/2}$, other approaches have been proposed, such as normalized residual activity (NORA), output efficiency (OE), pelvic excretion efficiency (PEE), and delayed images (2-7).

The objective of the present study is to analyze the applicability of late output fraction (LOF) in images acquired 3 hours after the administration of ^{99m}Tc-DTPA, in the evaluation of UPJO.

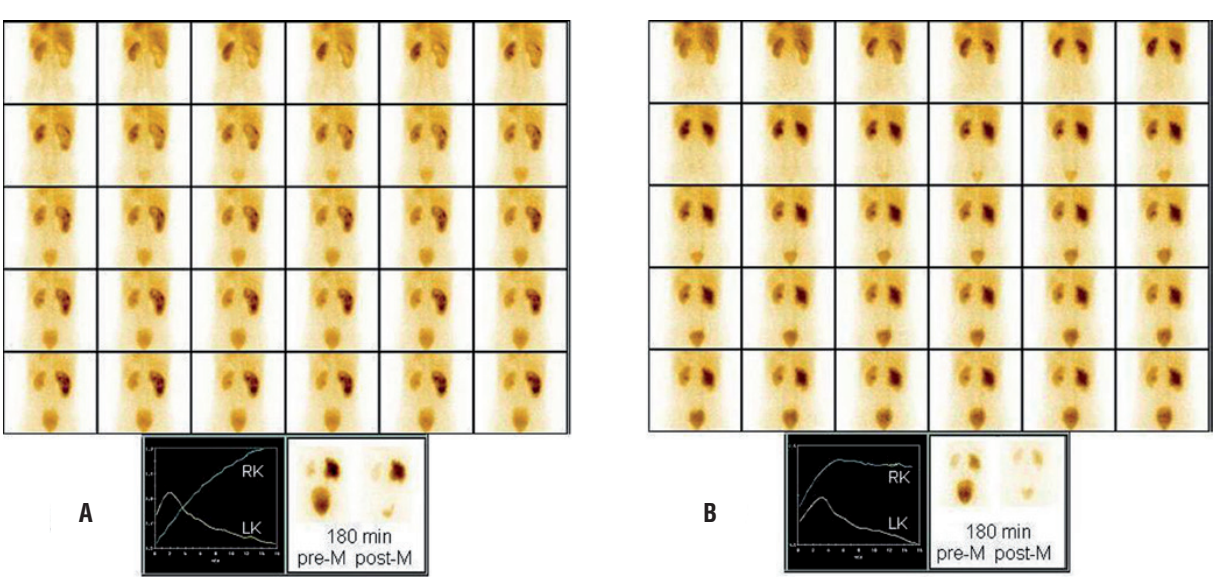
MATERIALS AND METHODS

The study has been approved by the Felicio Rocho Hospital's review board and the need for informed consent was waived. In the period between November 12th, 1997 and June 16th, 2014, 7,359 DYN were performed. The criteria for inclusion in the study were: at least two dynamic and static renal scintigraphy (pre and post-treatment), absence of other abnormalities such as duplication of excretion system, vesico-ureteral reflux, posterior ureteral valve, uretero-vesical junction obstruction and multicystic dysplastic kidney. 177 patients suspected to suffer from UPJO were included in the retrospective study. 58.8% (104/177) were male, and 41.2% (73/177) were female, constituting a total of 346 renal units (8 unilateral nephrectomies at first scan). Of the total number of renal units, 56.6% (196/346) were suspect for UPJO. Of these, 19.1% (66/346) units at right, and 25.4% (88/346) units at left side. In 21 patients, compromise was bilateral, corresponding to 12.1% (42/346) of the renal units. The mean ages were 4.3±3.8 years for the first, and 7.0±4.8 years for the second scan, with a follow-up of 2.7±2.5 years.

Relative renal function was evaluated by scintigraphy with ^{99m}Tc-DMSA, at a dosage of 37-74 MBq (1-2 mCi).

The DYN1 and DYN2 (the first and second dynamic renal scintigraphies, respectively) were acquired during a period of 20 minutes immediately after the intravenous injection of 74-185 MBq (2-5 mCi) of ^{99m}Tc-DTPA, with simultaneous administration of furosemide (1mg/kg of weight). Three hours after the administration of the radiopharmaceuticals, late pre and postvoid images were acquired (Figure-1). In the acquisition of the postvoid images, patients were maintained in an orthostatic position for 5 minutes, in order to contribute to renal emptying.

Figure 1 - Dynamic renal scintigraphy with 99mTc-DTPA with furosemide administration (F0) and late (180 minutes) premicturition (pre-M) and gravity assisted postmicturition (post-M) images.



A - preoperative: obstruction of the ureteropelvic junction (OJUP) in the right kidney by the criteria of renographic curve and decreases in kidney counts in the late images (LOF right kidney = -0.6%; LOF left kidney = 77.2%). **B** - after pyeloplasty: without OJUP (LOF right kidney = 83.9%; LOF left kidney = 82.6%).

The patients were orally hydrated 1 hour before the administration of the radiopharmaceuticals, with two or three cups of water for older children, and breastfeeding for infants. When possible, patients were requested to empty their bladders before beginning the scan. After the dynamic phase, the patients were kept hydrated for two hours more, through means of water intake (two or three cups) or breastfeeding. Older children were oriented to avoid micturition for 1 hour before the late images. The children without sphincter control, when presented for the 3 hour late images with bladder already empty, had acquired a "pre-void" image. They were maintained in standing position for 5 minutes, and following this, the "post-void" image was acquired.

The images were analyzed visually for the detection of any retention of the tracer in the renal calyces, pelvis or ureters, and renographic curves were drawn. Renal regions of interest (ROIs) were delineated in the last image of the dynamic sequence (20 minutes), and these ROIs were replicated in the late images both pre and postvoid, in order to estimate the radioactive renal activity.

The elimination phase in the renographic curves (phase 3) were initially classified from 0 to 6 (0 = adequate drainage, 1 = light fall in drainage, 2 = moderate fall in drainage, 3 = accentuated fall in drainage, 4 = practical absence of drainage, 5 = absence of drainage, 6 = accentuated hypofunction). For statistical analysis, the classification of renographic curves was summarized as follows: curves of type 0 to 3 were considered as non-obstructive and curves of type 4 and 5 as obstructive. Curves of type 6 did not permit the differentiation between non-obstructive and obstructive, and were thus considered not possible to be analyzed.

The fraction of elimination of the radiopharmaceutical in each renal unit was calculated using the equation: LOF (%) = (counts at 20 minutes – counts at 180 minutes) x 100 / counts at 20 minutes. For statistical analysis, obstruction was defined as a LOF of ≤12.4%, independent of the renographic standard.

Upon return for the second nuclear medicine evaluation, data was collected on the evolution of the patient, in particular the impression of the physician about the obstructive process and the treatment method chosen, clinical or surgical.

RESULTS

The distribution of scintigraphic diagnosis based upon evaluation of renal curves, for the first (CURVE 1) and the second (CURVE 2) studies, and upon renal counts at 20 minutes along with 180 minutes images for the first (LOF 1) and second (LOF2) studies, is presented in Table-1.

The analysis of CURVE 1 and LOF 1, in relation to the distribution by sex and affected side (Table-2) shows a higher incidence of obstructive process on the left side (Pearson Chi-Square $p<0.05$).

Clinical treatment was initiated in 71.1% (246/346), and surgical treatment instituted in 28.9% (100/346) of the renal units. Without considering contralateral renal units not suspect for obstruction, and thus considering only 196 renal units indicating clinical obstruction and renal curves with at least a moderate degree of delay in excretion, clinical treatment was the choice instituted in 52.6% (103/196) of cases, and pieloplasty in 46.9% (92/196) of cases. One kidney (0.5% - 1/196) with scintigraphic diagnosis of partial urine flow obstruction, and 22.1% of relative function in renal static scintigraphy, was nephrectomized. 2.0% (7/346) renal units were submitted to pieloplasty based upon suspect on clinical examination, without a scintigraphic diagnosis of obstruction. Table-3 shows the scintigraphic evaluations and treatments of the totality of the renal units studied. Measures of agreement Kappa of 0.428 ($p<0.001$) for CURVE 1 *versus* LOF 1, and of 0.221 ($p<0.001$) for CURVE 2 *versus* LOF 2 were found. In the comparison of DYN 1 and DYN 2, only for those patients submitted to conservative clinical treatment, measures of agreement Kappa of 0.158 ($p<0.001$) for CURVE1 *versus* LOF2, and of 0.512 ($p<0.001$) for (LOF1) *versus* LOF2 were found.

For the diagnosis based upon CURVE 1, a sensitivity of 100%, a specificity of 82.2%, a positive predictive value (PPV) of 10.4%, and a negative predictive value (NPV) of 100% were estimated. For the diagnosis based upon LOF1, a sensitivity of 100%, a specificity of 96.3%, a PPV of 35.7%, and a NPV of 100% were estimated.

Table 1 - Scintigraphic diagnosis.

Scan	Diagnostic criterion	Scintigraphic diagnosis
First	CURVE1	Unobstructed 65.9% (228/346)
		Obstructed 32.1% (111/346)
		Hypofunctioning* 2.0% (7/346)
	LOF1‡	Unobstructed 84.1% (291/346)
		Obstructed 15.9% (55/346)
Second†	CURVE2	Unobstructed 80.9% (279/345)
		Obstructed 17.7% (61/345)
		Hypofunctioning* 1.4% (5/345)
	LOF2‡	Unobstructed 96.2% (332/345)
		Obstructed 3.8% (13/345)

CURVE1 and 2: renal curves in the first and second scans.
LOF1 and 2: output fraction in the first and second scans.
*****severely hypofunctioning kidneys not allowing differentiation by curve analysis between obstruction and non obstruction.
† one unilateral nephrectomy between the first and second scintigraphy.
‡ a LOF ≤12.4% was considered as obstructive.

The study found 21.4% (74/346) renal units with ^{99m}Tc-DMSA relative function below 40.0%, and 78.6% (272/346) above 40.1%. Of the 74 units with relative function below 40.0%, 51.4% (38/74) were submitted to clinical treatment and 48.6% (36/74) to surgical treatment, while of the 272 units with relative function above 40.1%, 69.9% (190/272) were submitted to clinical treatment and 30.1% (82/272) to surgical treatment (p>0.05).

The therapeutic choice, clinical or surgical, and its relationship with scintigraphic diagnosis of obstruction *versus* non-obstruction is presented in Table-4.

DISCUSSION

The distinction between transitory dilation of drainage ducts and of UPJO is somewhat complex, and approaches vary widely among institutions. No study is considered to be a gold standard in the evaluation of obstructive renal processes (1-2).

Though the analysis of renal curves, including the calculation of $T_{1/2}$, and the use of other indicators (OE and NORA) (6, 8) are the most common approaches, the acquisition of late pre and postvoid gravity assisted images have been considered useful (3, 7, 9, 10). $T_{1/2}$ is no longer conside-

Table 2 – Distribution of diagnosis of the obstructive type for affected side and sex.

Diagnostic criterion	Side*	Sex	Renal units
CURVE1 32.7% (111/339)	Right 39.6% (44/111)	Boys	59.1% (26/44)
		Girls	40.9% (18/44)
	Left 60.4% (67/111)	Boys	68.7% (46/67)
		Girls	31.3% (21/67)
LOF1† 15.9% (55/346)	Right 36.4% (20/55)	Boys	50.0% (10/20)
		Girls	50.0% (10/20)
	Left 63.6% (35/55)	Boys	65.7% (23/35)
		Girls	34.3% (12/35)

CURVE1: renal curves in the first scan.
LOF1: output fraction in the first scan.
* Pearson Chi-Square $p< 0.05$
† a LOF ≤12.4% was considered as obstructive.

red sufficient in the evaluation of renal drainage (10-12). Frequently, late pre and postvoid images contradict curves indicating obstructive pattern, and also supply more consistent and reproducible data than renogram (2, 13). This may explain the relatively low correlation found between renal curves and LOF by the Kappa agreement analysis.

LOF is an attempt to evaluate renal draining considering renal counts at 20 minutes and at 3 hours pre and postvoid images after ^{99m}Tc-DTPA and furosemide injections. For OE and NORA the ideal length of time for the realization of late images varies with MTT (6). For smaller MTT, pre and postvoid images at 60 minutes are probably sufficient, while for larger MTT, later images might be necessary. Late images at 60 and 120 minutes were attempted to calculate LOF before 180 minutes was considered more reliable. LOF incorporates the additional advantages of postmicturition images replacing bladder catheterization (2, 3). OE has less dependence on the level of renal function (2) and LOF seems to work well even in cases of reduced renal function.

The cutoff point which characterizes obstruction *versus* non-obstruction, by means of LOF, was defined as experience was gathered. A LOF of up to 10% is strongly indicative of UPJO, while a LOF greater than or equal to 15% is indicative of a non-obstructive process, with >10% and <15% being in the range of uncertainty. In the present study, for effects of statistical analysis, values of ≤12.4% were used as indicators of urinary flow obstruction. In practice, the criteria for defining a diagnosis as obstructive has been LOF ≤10%, and to disregard obstruction, LOF ≥25%. For the values >10% e <25%, a new study is recommended after 6 months for the sake of certainty.

In the estimation of diagnostic capacity of the criteria utilized in the present study, the second dynamic renal scintigraphy of the group submitted to clinical treatment was used. Both clinical impression and the results obtained through LOF2

Table 3 – Pre and post-treatment scintigraphic evaluation in all renal units studied.

Diagnostic criterion (pretreatment)	Scintigraphic diagnosis (pretreatment)	Treatment	Diagnostic criterion (post-treatment)	Scintigraphic diagnosis (post-treatment)
	Unobstructed 57.2% (198/346)			Unobstructed 100% (198/198)
CURVE1	Obstructed 13.9% (48/346)		LOF2*	Obstructed 10.4% (5/48)
		Clinical		
	Unobstructed 67.1% (232/346)			Unobstructed 100% (232/232)
LOF1*	Obstructed 4.0% (14/346)		LOF2*	Obstructed 35.7% (5/14)
	Unobstructed 8.7% (30/346)			Unobstructed 100% (30/30)
CURVE1	Obstructed 20.2% (70/346)		LOF2*	Obstructed 11.4% (8/70)†
	Unobstructed 17.1% (59/346)	Pyeloplasty		Unobstructed 89.8% (53/59)
LOF1*			LOF2*	
	Obstructed 11.8% (41/346)			Obstructed 4.9% (2/41)†

CURVE1: renal curves in the first scan.
LOF1 and 2: late output fraction in the first and second scans.
* a LOF ≤12.4% was considered as obstructive.
† 40 renal units undergoing pyeloplasty and one nephrectomy.

Table 4 – Relationship between the scintigraphic diagnosis and treatment established in clinical suspicion of UPJO.

Scintigraphic criteria and diagnosis (pretreatment)		Treatment	
CURVE1	LOF1*	Clinical	Pyeloplasty
Unobstructed	Unobstructed	88.6% (195/220)	11.4% (25/220)
Obstructed	Obstructed	23.4% (11/47)	76.6% (36/47)
Unobstructed	Obstructed	37.5% (3/8)	62.5% (5/8)
Obstructed	Unobstructed	52.1% (37/71)	47.9% (34/71)

CURVE1: renal curves in the first scan.
LOF1: output fraction in the first scan.
***** a LOF ≤12.4% was considered as obstructive.

were, together, considered to be the true diagnosis for the definition of obstruction *versus* non-obstruction. After a mean follow-up time of 2.7±2.5 years, if an unobstructive diagnosis by DYN1 were in error, a significant deterioration in renal function would have been expected, which did not occur. As such, it is reasonable to think that the DYN1 diagnosis was correct. The option to utilize LOF2 and not CURVE2 was due to the apparently better discrimination of obstruction *versus* non-obstruction permitted through LOF, compared to renal curves, as has already been observed with late pre and postvoid images (2, 13).

In the group submitted to clinical treatment, the rate of non-obstructive diagnosis was 57.2% (198/346) for CURVE1 and 67.1% (232/346) for LOF1. These diagnosis proved true in DYN2, with 100% of non-obstruction for both groups, that is, a larger number of non-obstructions through LOF1 criteria when the natural evolution of the cases is considered as a true result.

Only 10.4% (5/48) of cases diagnosed as obstructive through renal curves, and 35.7% (5/14) of cases diagnosed as obstructive through LOF, which were submitted to clinical treatment, presented signs of obstruction at second study. This data, in addition to demonstrating the higher specificity of diagnosis based upon LOF, appear to reflect that hydronephrosis caused by UPJO is a mutable process through time, possibly more functional than anatomical, and may thus cure spontaneously (13-18).

When considering the group of 220 renal units with very clear scintigraphic diagnosis, that is, curves and LOF frankly non-obstructive, it was observed that 11.4% (25/220) were submitted to pyeloplasty. On the other hand, in the group of 47 renal units with scintigraphic diagnosis, curves and LOF clearly obstructive, it was observed that 23.4% (11/47) were submitted to clinical treatment. No statistically significant difference was encountered in the choice of treatment as a result of relative renal function, estimated through ^{99m}Tc-DMSA, below or above 40.0%. These data reflect the current lack of a standard in the choice of conduct (1, 2, 13). 10.2% (6/59) of renal units with diagnosis non-obstructive through LOF, submitted to surgical treatment, evolved into an obstructive pattern, suggesting that they were damaged by an inadequate intervention.

Further studies are necessary in order to identify which kidneys with detected ANH are at risk for deterioration in their function, which will permit more certainty in the choice of treatment. In any case, from the data presented, the diagnosis of urinary drainage obstruction based on LOF was superior to diagnosis based upon renal curves, and provided higher certainty in the indication of conservative treatment in about 17.2% of the patients whose LOF indicated absence of obstruction while renal curve suggested an obstructive process.

CONCLUSIONS

This study to evaluate urinary flow obstruction utilizing dynamic renal scintigraphy with ^{99m}Tc-DTPA demonstrated that an LOF of up to 10% is indicative of UPJO, while an LOF equal to or above 15% is not indicative of an obstructive process. The data showed that LOF provides equivalent sensitivity and NPV and higher specificity and PPV compared with renal curve based diagnosis, and is useful in the evaluation and follow-up of suspected cases of UPJO.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Durasphere® EXP: a non-biodegradable agent for treatment of primary Vesico-Ureteral reflux in children

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ABSTRACT

Introduction: Durasphere® EXP (DEXP) is a compound of biocompatible and non-biodegradable particles of zirconium oxide covered with pyrolytic carbon. The aim of this study is to evaluate the durability of off-label use of DEXP in the treatment of primary vesicoureteral reflux in children.

Materials and Methods: Patients who underwent subureteric injection of DEXP for the correction of primary VUR were retrospectively reviewed . Patients aged >18 years as well as those who had grade-I or -V VUR, anatomic abnormalities (duplicated system, hutch diverticulum), neurogenic bladder or treatment refractory voiding dysfunction were excluded. Radiologic success was defined as the resolution of VUR at the 3rd month control. Success was radiographically evaluated at the end of the first year.

Results: Thirty-eight patients (9 boys, 29 girls; mean age, 6.3±2.7 years) formed the study cohort. Forty-six renal units received DEXP (grade II: 22; grade III: 18; grade IV: 6). Mean volume per ureteric orifice to obtain the mound was 0.70±0.16mL. First control VCUG was done after 3 months in all patients. After the first VCUG, 6 patients had VUR recurrence. Short-term radiologic success of DEXP was 84.2%. Rate of radiologic success at the end of the first year was 69.4% (25/32). Lower age (p:0.006) and lower amount of injected material (p:0.05) were associated with higher success rates at the end of 1 year.

Conclusion: This is the first study to assess the outcomes of DEXP for treatment of primary VUR in children. After 1 year of follow-up, DEXP had a 69.4% success rate.

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INTRODUCTION

Vesicoureteral reflux (VUR) is a challenging problem in pediatric urology. Treatment options include close observation, continuous antibiotic prophylaxis, endoscopic subureteric injection, and open/robotic ureteric re-implantation. Urinary tract infections (UTIs) concomitant with VUR can lead to renal scarring and hence hypertension and renal failure (1). Treatment aim is to prevent febrile UTIs.

Subureteric injection of bulking agents has been shown to be a good alternative to ureteric re-implantation. The success of endoscopic treatment is dependent not only to the features of the bulking agent but also grade of VUR, presence of lower urinary tract dysfunction (LUTD) and anatomical abnormalities. The initial substance to be

used was Teflon™ while dextranomer/hyaluronic acid (Dx/HA) was the first agent to be approved by the US Food and Drug Administration (FDA) for VUR treatment in children in 2001. Since then, Dx/HA has been used widely for the correction of low-grade VUR and has become the "gold standard". The migration risk of Teflon, reduced prevalence of overall success (77%) and a relatively high prevalence of recurrence of Dx/HA (11-26%) have had pivotal roles in the development of new bulking agents with better outcomes (2). Subsequently, several non-biodegradable agents (carbon-coated particles of zirconium oxide, polyacrylamide hydrogel (PAHG), polyacrylate/polyalcohol copolymer (PPC)) have been released on the market. Long-term durability of those materials used in subureteric injection is linked to their non-biodegradability and formation of fibrotic capsules (3).

Another non-biodegradable agent, Durasphere® EXP (DEXP) has been actively used in urological practice since 1999 to treat stress urinary incontinence in women. Here, we evaluated the durability of off-label use of Durasphere® EXP (DEXP) for the treatment of primary VUR in children.

MATERIALS AND METHODS

The injectable bulking agent DEXP (Carbon Medical Technologies, St. Paul, MN, USA) is a compound of biocompatible and non-biodegradable particles of zirconium oxide covered with pyrolytic carbon suspended in a water gel with 2.8% beta-glucan (4). It is a bulking agent used (off-label) for VUR correction in children. Furthermore, it has been used in our daily practice between 2008 and 2013.

After obtaining local review board approval, medical files of patients who had undergone subureteric injection of DEXP for correction of primary VUR in our clinic between February 2008 and March 2013 were reviewed retrospectively. Age, sex, presenting symptoms, laterality and degree of VUR (classification set by the International Reflux Study Committee), presence of renal scars in DMSA (Di-Mercapto-Succinic Acid) scintigraphy, volume of injected material, and previous intervention for VUR were noted. Patients aged >18 years as well as those who had VUR grade I or V, anatomic abnormalities (duplicated system, hutch diverticulum), neurogenic bladder or voiding dysfunction refractory to appropriate medical treatment were excluded (Figure-1). All patients had written informed consent prior to surgery.

Endoscopic procedures were performed after a sterile urine culture was obtained in all patients. Subureteric injection was undertaken under general anesthesia using a 9.5-Fr, 6° pediatric cystoscope (Karl Storz Endoscopy, Slough, UK) with a metal 3.7-channel, 20-G, pencil point-tip needle (254mm or 381mm) by two surgeons (A.Y.M., U.O.). DEXP was applied using the STING/hydrodistention method. All patients were discharged after spontaneous voiding on the day of the procedure. Patients were continued on their previously started antibiotic prophylaxis until the first voiding cystourethrogram (VCUG) at 3-month follow-up. Radiologic success was defined as the resolution of VUR at the 3rd month control VCUG. The durability of success in those patients was radiographically and clinically evaluated at the end of the first year.

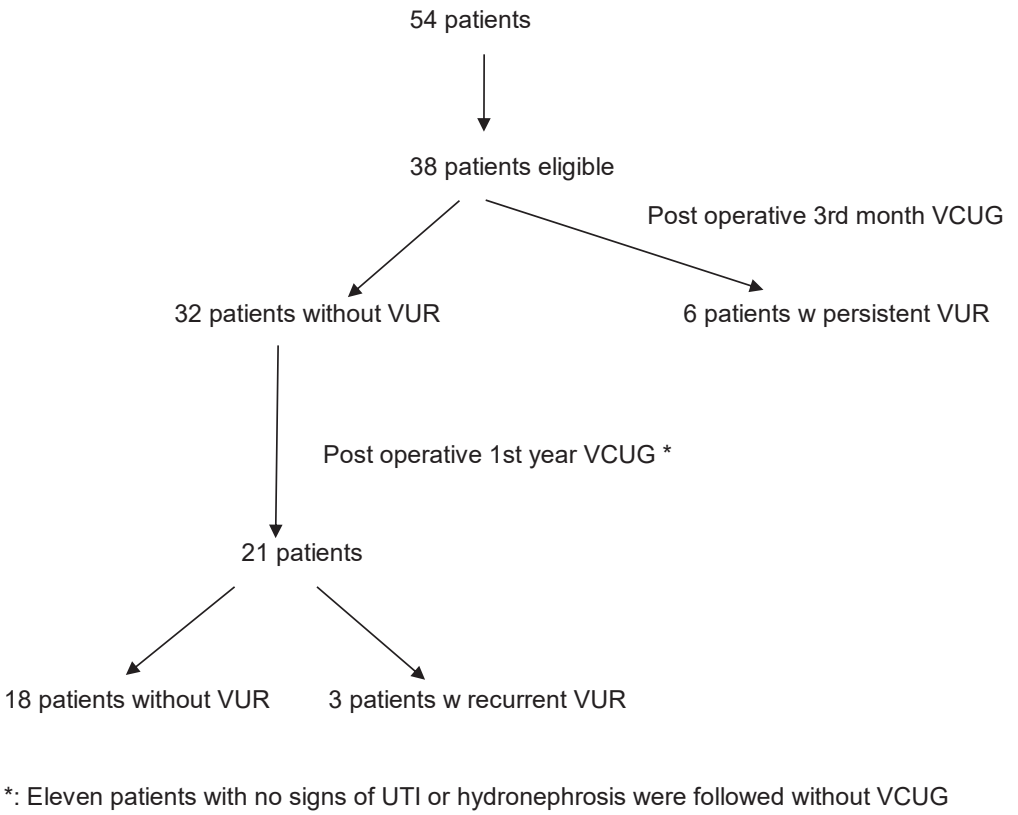
Statistical analysis

The normality hypothesis of the variables was examined by the Shapiro Wilk test. The group comparisons between the categorical variables were analyzed using Kruskall Wallis test and Dunn test was applied for subsequent multiple comparisons (Post-hoc). The comparison of the qualitative variables was done using the Fisher Freeman-Halton test. Statistical analyzes were performed using SPSS Version 21 software.

RESULTS

Thirty-eight patients (9 boys, 29 girls; mean age, 6.3±2.7 years) and 46 renal units were treated with DEXP. Indications for subureteric injection were recurrent febrile UTI in 25 patients, VUR and renal scarring (in DMSA scintigraphy) in 10 patients, and non-resolving VUR at the follow-up for antenatal hydronephrosis in 3 patients. VUR was unilateral (13 right, 17 left) in 30 patients and

Figure 1 - Flow diagram of patients.



bilateral in 8 patients. Ten patients had received two subureteric injections previously using Dx/HA, whereas 28 received their first subureteric injection. A total of forty-six renal units received DEXP (grade II: 22; grade III: 18; grade IV: 6). Mean volume per ureteric orifice in order to obtain the mound was 0.70±0.16mL. First control VCUG was undertaken after 3 months in all patients. After the first VCUG, 6 patients (2 bilateral, 4 unilateral disease previously) had failure. Thus, the 3-month radiologic success rate was 84.2% (Table-1).

During the follow-up of the patients with no VUR at 3-months, 1 patient had febrile UTI. Imminent VCUG revealed VUR recurrence (pretreatment unilateral grade-IV VUR, one patient was lost to follow-up). First-year control VCUG showed that 4 out of 29 patients had VUR recurrence. Of those with recurrent VUR, one patient had bilateral grade-III VUR and renal scarring preoperatively. The grade of VUR was downgraded to bilateral grade 2. Also, 1 had bilateral grade-III VUR, 1 had unilateral grade-III VUR and 1 had unilateral grade IV VUR, previously. However, all of those patients were infection and LUTD free. Radiologic success at the end of the first year was 69.4%.

Nine patients (9 renal units) without VCUG at 1 year were accepted as clinically successful since they were UTI and LUTD free. Success at 1st year was higher in the patients with lower age (5.64 vs. 9.66, p:0.006) and less amount of injected material (0.66 vs. 0.75, p: 0.05).
Moreover, presence of renal scar and presentation with recurrent UTI were the risk factors for reduced success rate (both p:0.023). The ratios and significance of variables are given in Table-2.

After surgery, 1 patient had a transient de novo hydronephrosis without functional loss according to scintigraphy. In addition, ten patients had a mean follow-up of >3 years without any sign of a UTI or urinary obstruction.

Table 1 - Results of injection of Duraspehere® EXP according to grades of vesicoureteral reflux.

Preoperative VUR	VCUG 3 months after surgery	VCUG 1 year after surgery
(n: Renal Unit)	(VUR/no VUR Renal Unit) Success (%)	(VUR/no VUR Renal Unit) Success (%)
Grade-II VUR	2/20	2/10
n=22	90.9%	83.3%
Grade-III VUR	4/14	2/4
n=18	77.7%	66.6%
Grade-IV VUR	2/4	1/1
n=6	66.6%	50%

DISCUSSION

Biodegradable synthetic materials have a high rate of reabsorption over time. Dx/HA is included in this group, and its rate of recurrence in long-term follow-up studies has been reported to be 11-26% (5). It has been suggested that non-biodegradable synthetic materials become more persistent by forming a fibrotic capsule. Such materials available currently are carbon-coated particles of zirconium oxide, PAHG and PPC.

Durasphere® was introduced as a biocompatible, non-migrating, non-erosive, non-immunogenic, non-biodegradable substance comprising large (212-500 microns) carbon-coated particles of zirconium oxide. In 1999, it was approved by the US FDA for the treatment of stress-type urinary incontinence caused by sphincter insufficiency in

Table 2 - Ratio comparison of categorical and continuous variables (Fisher Fremann-Halton test).

	No VUR at 3rd and 12th months (%)	No VUR at 3rd month but VUR at 12th month (%)	p value
Gender			
Male	29	0	0.3
Female	71	100	
Type of presentation			
UTI	67	16.7	
VUR + Renal scar	29	50	**0.023**
Antenatal hydronephrosis f/u	3.2	33.3	
Laterality			
Right	38.7	50	0.49
Left	61.3	50	
Degree of VUR			
Grade II	58	33.3	0.29
Grade III	35.5	33.3	
Grade IV	6.5	33.3	
Presence of renal scar			
No	71	16.7	**0.023**
Yes	29	83.3	
Age (years)	5.6	9.6	**0.006**
Injected volume (mL)	0.66	0.75	**0.05**

women. Its production was discontinued because of its high viscosity (which caused difficulties in injection) and because patients had asymptomatic migration of lymph and formation of sterile pseudo-abscesses after periurethral injection. The manufacturer replaced the product with a substance of smaller-sized particles (90-212 microns) under the name "Durasphere® EXP" (6).

Some authors have linked these unwanted complications of DEXP with injection of excessive amounts of DEXP into the periurethral region as well as injection of DEXP into blood vessels (7). Prevalence of formation of sterile pseudo-abscesses in transurethral injection of Dx/HA has been reported to be 16% (8). It is not known if this new product causes migration or pseudo-abscess formation if used in smaller amounts.

In a study comparing the persistency of Durasphere® with collagen in women with urinary incontinence, long-term results were better for Durasphere® than for collagen (9). However, the effect of Durasphere® was reduced over time. How the effect persists over time in VUR treatment is not known.

Several studies have evaluated the use of non-biodegradable substances in VUR treatment. However, the number of studies focusing on off-label use of DEXP in VUR treatment is small. In our country, off-label use of DEXP has been for the treatment of VUR in children since 2006 (10).

In 2011, it was reported that the prevalence of clinical success of DEXP for treatment of recurrent transplant pyelonephritis secondary to VUR to the transplant kidney in 8 patients was 75% during a period of follow-up of 3-52 months, but the of long-term efficacy of DEXP treatment was not reported (11).

Evaluation of success of endoscopic treatment can be done by clinical (urine culture) and radiologic (VCUG, ultrasonography) means, as well as by scintigraphy. We found the rate of short-term (3 months) radiologic success of DEXP to be 81.3% (32/38). Rate of radiologic success at the end of the first year was 69.4% (25/32). Our results indicated that durability of success is significantly higher in younger children and lower VUR degree. Additionally, achieving the intended amount of mound using as little injection material as possible was found to be associated with long-term success.

The short-term success of non-biodegradable PAHG for endoscopic treatment of VUR was shown to be 81.2%. The authors found at the second injection that the mound obtained with PAHG at first injection was flattened or displaced, and that the fluidity of PAHG could be the reason for such failures (5). In our study, we observed medially displacement of the material in 2 of 3 recurrent cases.

PPC was shown to have good overall success in VUR treatment (83.6-95%) (12). Recurrent VUR was not reported in 140 patients (106 of these patients had a control VCUG) during a follow-up >3 years (12). Some authors argue that PPC injection carries a great risk of ureterovesical obstruction, and recommended close monitoring after surgery (13).

In our study, de novo hydronephrosis or a UTI were not observed in 10 cases who had a follow-up of 3 years. Postoperatively, 1 patient had a transient de novo hydronephrosis without functional loss according to scintigraphy and the hydronephrosis resolved eventually. The decrease of success in time may be related to the substance itself as well as patient related factors (undiagnosed bladder dysfunction, lack of muscular support at the level of ureteral hiatus). This finding confirms that biodegradability may not be the scapegoat for reflux recurrence after endoscopic injection.

One important aspect of the material was the rapid clotting potential. If the initial puncture was not in the right sub-mucosal plane or the needle faces some resistance, carbon particles may not find their route and the water-based carrier gel component of the material goes through the needle. If that happens, the carbon particles would no longer flow through the needle that necessitate a brand-new needle and injection material to be used.

Our study was limited due to its retrospective nature. In addition, the prevalence and type of complications were not reported. The sustainability of the ureteric mound could have been measured during control urinary ultrasonography.

CONCLUSIONS

This is the first study on the 1-year outcomes of DEXP for endoscopic treatment for primary VUR in children. DEXP had a durability of 69.4%. Our results reveal that biodegradability of the injected material is not the sole factor for the late recurrence of endoscopic treatment of VUR. Further prospective, randomized controlled trials with long-term results are needed to determine the efficacy and durability of DEXP for VUR treatment.

COMPETING INTERESTS

Ethical Standard: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Formal consents were obtained from parents.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Preoperative care of Polypoid exposed mucosal template in bladder exstrophy: the role of high-barrier plastic wraps in reducing inflammation and polyp size

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ABSTRACT

Objective: To assess the role of high-barrier plastic wrap in reducing the number and size of polyps, as well as decreasing the inflammation and allergic reactions in exstrophy cases, and to compare the results with the application of low-barrier wrap.
Materials and Methods: Eight patients with bladder exstrophy-epispadias complex (BEEC) that had used a low density polyethylene (LDPE) wrap for coverage of the exposed polypoid bladder in preoperative care management were referred. The main complaint of their parents was increase in size and number of polyps. After a period of 2 months using the same wrap and observing the increasing pattern in size of polyps, these patients were recommended to use a high-barrier wrap which is made of polyvinylidene chloride (PVdC), until closure. Patients were monitored for the number and size of polyps before and after the change of barriers. The incidence of para-exstrophy skin infection/inflammation and skin allergy were assessed. Biopsies were taken from the polyps to identify histopathological characteristics of the exposed polyps.
Results: The high barrier wrap was applied for a mean ± SD duration of 12±2.1 months. Polyps' size and number decreased after 12 months. No allergic reaction was detected in patients after the usage of PVdC; three patients suffered from low-grade skin allergy when LDPE was applied. Also, pre-malignant changes were observed in none of the patients in histopathological examination after the application of PVdC.
Conclusion: Polyps' size and number and skin allergy may significantly decrease with the use of a high-barrier wrap. Certain PVdC wraps with more integrity and less evaporative permeability may be more "exstrophy-friendly".

ARTICLE INFO

Keywords:
Bladder Exstrophy; Cosmetics; Infection; Polyps

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INTRODUCTION

Bladder exstrophy epispadias complex (BEEC) is an uncommon congenital abnormality. The prevalence of classic bladder exstrophy is approximately 1 in 50,000 live births (1). In these affected patients, the gross appearance of the bladder template, especially in the setting of polyp formation, is a major concern for the surgeon. The exact history of these polyps has not yet been documented, since many patients are born with polyps; while some seem to form later, or at least to present growth later. Concern of premalignant lesions may rise by the polypoid manifestation of the exstrophic bladder template (2). It should be also mentioned that patients can confront with more severe epithelial injury in the presence of cystitis glandularis in polyps excised during repeat or delayed primary closure (3).

At birth, the sensitive exposed bladder mucosa should be covered with a non-adherent film (Plastic Wrap) to prevent infection and sticking of the bladder to diapers or clothing (4). Low density polyethylene (LDPE) attracted the attentions as a sustainable and environmentally acceptable plastic wrap. However, the barrier quality to oxygen, aroma, microorganisms, and flavor molecules of LDPE is not as sufficient as polyvinylidene chloride (PVdC) which is also known as Saran wrap. In spite of the fact that US Saran wrap is PVdC-free, it still appears in other forms. Nevertheless, the water vapor transmission rate (WVTR) of PVdC is significantly lower than LDPE (5, 6).

Due to the importance of applying a proper wrap during the preoperative period and the role of environmental factors in polyps' formation, we decided to evaluate the clinical outcome of two different wraps (LDPE and a high-barrier wrap which is made of PVdC) in eight BEEC cases. This type of wrap with molecules bound so tightly together is supposed to act as a high barrier against oxygen, moisture, chemicals and environmental contamination. The size and the number of polyps, infection and skin allergy of the exposed polypoid bladder area, and the histopathological changes of exposed polyps were evaluated after the application of these two wraps in preoperative period.

MATERIALS AND METHODS

Eight patients with BEEC in the setting of polyp formation were referred for delayed bladder closure from district hospitals around the country from February 2012 to April 2014. Children with failed attempts were excluded from this study. Parents of all children complained of increase in the number and size of polyps during the application of LDPE for coverage of the exposed bladder before being referred to our center. However, the exact size of polyps was not measured. Considering the bladder protrusion during early growth, it may not be that easy for parents to truly determine the number and size of polyps. So, after institutional review board approval and obtaining informed consent, the same wrap was used for a period of 2 months. After confirmation of increase in the number and size of polyps while applying LDPE, we recommended the use of a high-barrier wrap which is made of PVdC in the preoperative care until the time of closure. The same area of surrounded skin was covered with both wraps in order to evaluate any possible skin allergy by the application of these plastic wraps.

This non-adherent wrap was applied for the coverage of the polypoid bladder to prevent clinging of the bladder to diapers or clothing until the patient was ready to undergo closure. The plastic wraps were removed at the time of diaper change and the bladder was irrigated with sterile saline. After wiping the bladder, a clean PVdC wrap was placed. Patients were regularly evaluated for determining the number and size of polyps. Personal interviews, monthly visits for checking the bladder plate, and photographic evaluations were made to access the status of the patients regarding the number and size of polyps as well as skin allergy to the wraps. The number of polyps was precisely evaluated by a single urologist during each follow-up. In spite of the fact that the size of polyps was unchangeable in different situations of bladder plate in a same time-point, the bladder template was examined while the patient was calm, the internal abdominal pressure was not increased, and the bladder was not notably protruded in order to decrease any measurement bias.

To evaluate the histopathological characteristics of the exposed polyps, biopsies were taken from the polyps of these patients at initial visit before the application of PVdC (during the first examination under anesthesia (EUA) for bladder plate measurement) and during the bladder closure (after one year of PVdC application). H&E staining was performed and the samples were analyzed by a pathologist who was totally blind to the study.

Approximation of the symphysis pubis without osteotomy was performed in all of these children according to the previously described techniques (7, 8). Moreover, sub-urothelial polyp nucleation resection and urothelial auto-augmentation cystoplasty were performed according to our recent article (9).

RESULTS

In this study, eight children with BEEC in the setting of polyp formation (5 boys and 3 girls) with a mean ± SD age of 4.21±1.53 years (range 1 to 7) were enrolled. In all patients LDPE was applied from birth until being referred to our center. The mean ± SD duration of applying the new high barrier wrap (PVdC) was 12±2.1 months. The incidence of skin allergy decreased after the application of PVdC. In fact, 3 out of 8 patients (37.5%) experienced a low grade skin allergy when LDPE was applied in preoperative care (mild redness and swollen skin at the point of contact with the wrap); while no skin allergy was observed in none of the participants when the wrap was replaced with PVdC (Table-1).

The number of polyps decreased in 3 patients when LDPE was replaced with PVdC (Table-1). In addition, the size of polyps decreased in all children after the application of PVdC. Figures 1-3 show the difference between the area dimensions of polyps before and after PVdC application in two different patients. Total area of polyps in each patient before and after application of PVdC is summarized in Table-1. Accordingly, even in patients with no decrease in the number of polyps, total area of polyps decreased after the application of a high barrier wrap.

Parents were more satisfied with the application of PVdC because of the absence of infection or allergic reaction as well as a decrease in the number and size of the polyps before surgical intervention.

Histological evaluation of the biopsies taken from the polyps showed similar pathological features while applying LDPE or PVdC wrap with no significant difference. No fibrosis, edematous, cystitis cystic, or cystitis glandularis pattern were detected in none of the patients applying this wrap after one year before closure (Figure-4).

DISCUSSION

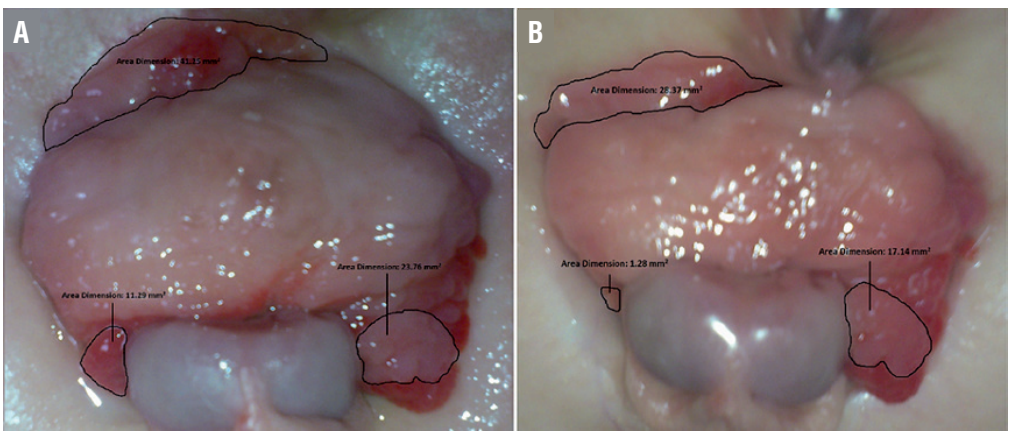
The findings of the current study confirmed that the microstructural characteristics of wraps is an important factor in decreasing the size and number of polyps before surgical intervention. However, the histopathological changes are similar with the application of different wraps. Polypoid bladder template is an important concern in patients with BEC with different ages. So, the wide range of participants in this study may not confound the results.

Proponents of complete primary repair of BEEC suggested that this treatment can allow for one-stage repair as well as stimulating early bladder growth (10). Bladder polyps are one of the factors contributing to an unsuitable template for immediate closure (2). In addition, bladder exstrophy template with multiple polyps is more susceptible to potential environmental carcinogens. So, it is clear that the bladder template should be previously covered during the preoperative period.

Table 1 - comparison of skin allergy, number and size of polyps before and after the application of a high barrier plastic wrap.

Case number	Number		Total area(mm^2)		Skin allergy	
	Before	After	Before	After	Before	After
No. 1	5	5	11.32	8.54	+	-
No. 2	6	5	13.35	9.21	+	-
No. 3	4	4	10.76	8.12	-	-
No. 4	5	4	10.98	6.71	-	-
No. 5	4	4	11.06	7.52	-	-
No. 6	5	4	12.13	8.09	+	-
No. 7	3	3	9.62	7.54	-	-
No. 8	5	5	11.24	9.83	-	-

Figure 1 - Significant decrease in the size of polyps before (A) and (B) after the application of PVdC in patient A.



Decrease in size and number of polyps may result in better postoperative results. In spite of the fact that excision remains superficial, large and numerous polyps may impart further weakness to the bladder after closure of the remaining mucosal defect with absorbable suture. In spite of sufficient protection during the preoperative period, polyps may form or worsen. So, application of an exstrophy-friendly coverage is obviously of great importance.

The polypoid appearance of bladder exstrophy may raise the concern of premalignant lesions. In one study, the microscopic slides of bladder exstrophy cases undergoing polyp's excision at the time of bladder wall closure were reviewed (2). In 6 out of 24 patients with primary bladder closure, two types of fibrotic and edematous polyps were observed, which were associated with overlying reactive squamous metaplasia. Comparing polyps resected during primary versus secondary closure, the occurrence of cystitis cystic and cystitis glandularis were higher in secondary closure. However, according to the histological evaluation of our recent study, no sign of metaplasia or dysplasia was observed in none of the patients treated with either sub-urothelial polyp nucleation resection and urothelial auto-augmentation cystoplasty or simple excision of the polyps and bladder closure (9). It is well known that fibrous polyps are associated with profuse angiogenesis within the connective tissue stroma. However, the angiogenesis was within the normal range in the biopsies taken from both groups (9) which can allow us to apply the sub-urothelial polyp nucleation resection and urothelial auto-augmentation cystoplasty. The results of the present study were compatible with the outcomes of our previous paper, in which no sign of fibrosis, edematous, cystitis cystic, or cystitis glandularis pattern was detected in the excised polyps. However, more long-term follow-ups are underway to evaluate the postoperative histopathological characteristics of these patients.

With much of the recent interest focused on improved cosmesis after the primary bladder reconstruction, little attention has been dedicated to reduce the size and number of polyps and prevent further inflammation before the operation. In several studies, it has been demonstrated that the application of a barrier dressing and frequent irrigation can preserve the bladder mucosa (11, 12). In one study in 2015, it has been demonstrated that plastic coverage during all follow-up period prevented the thickening of the mucosa and polyp formation and prevented prolonged environmental exposure of the bladder mucosa (13). In the present study, it was shown that the application of PVdC as an appropriate wrap may decrease the size and number of polyps. As an important consequence, these patients may be able to benefit

Figure 2 - Significant decrease in the size of polyps after the application of PVdC over a period of 15 months.

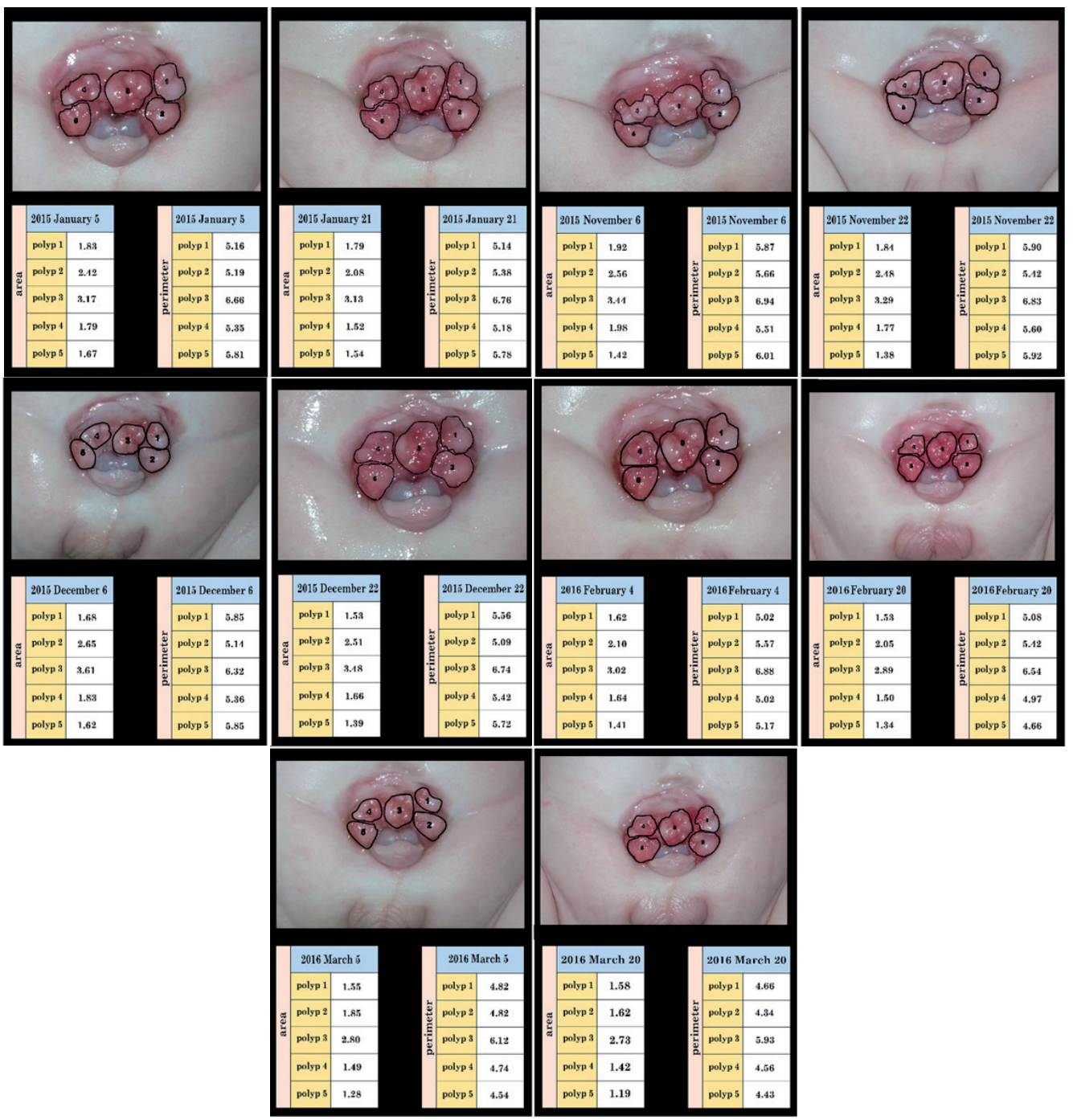
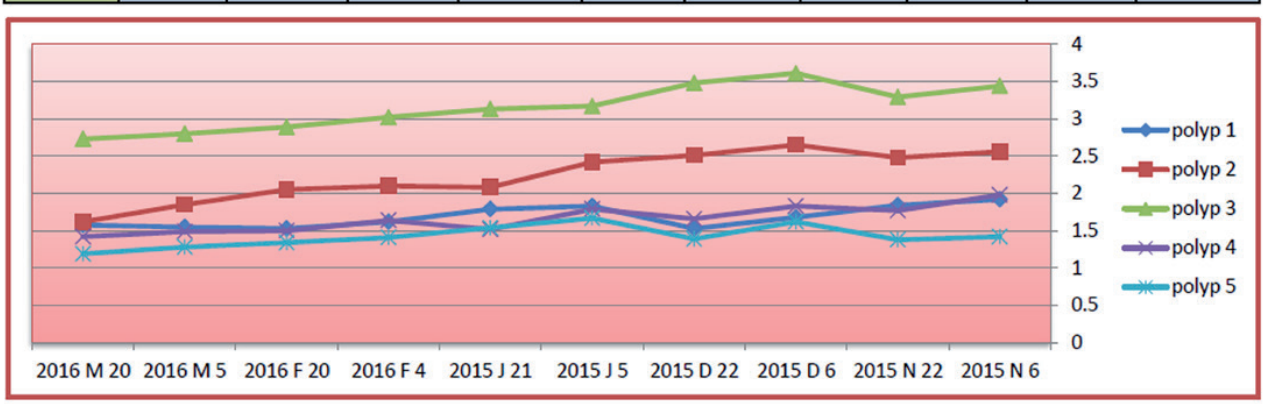


Figure 3 - Curves of the perimeter and area of each polyp during a period of 15 months in patient B.

Area	2015 N 6	2015 N 22	2015 D 6	2015 D 22	2015 J 5	2015 J 21	2016 F 4	2016 F 20	2016 M 5	2016 M 20
polyp 1	1.92	1.84	1.68	1.53	1.83	1.79	1.62	1.53	1.55	1.58
polyp 2	2.56	2.48	2.65	2.51	2.42	2.08	2.1	2.05	1.85	1.62
polyp 3	3.44	3.29	3.61	3.48	3.17	3.13	3.02	2.89	2.8	2.73
polyp 4	1.98	1.77	1.83	1.66	1.79	1.52	1.64	1.5	1.49	1.42
polyp 5	1.42	1.38	1.62	1.39	1.67	1.54	1.41	1.34	1.28	1.19



perimeter	2015 N 6	2015 N 22	2015 D 6	2015 D 22	2015 J 5	2015 J 21	2016 F 4	2016 F 20	2016 M 5	2016 M 20
polyp 1	5.87	5.9	5.85	5.56	5.16	5.14	5.02	5.08	4.82	4.66
polyp 2	5.66	5.42	5.14	5.09	5.19	5.38	5.57	5.42	4.82	4.34
polyp 3	6.94	6.83	6.32	6.74	6.66	6.76	6.88	6.54	6.12	5.93
polyp 4	5.51	5.6	5.36	5.42	5.35	5.18	5.02	4.97	4.74	4.56
polyp 5	6.01	5.92	5.85	5.72	5.81	5.78	5.17	4.66	4.54	4.43

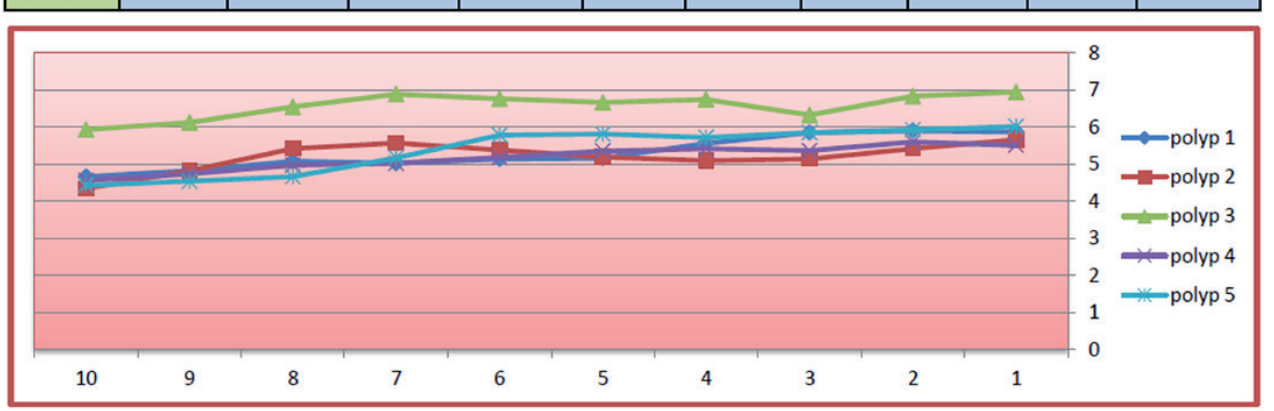
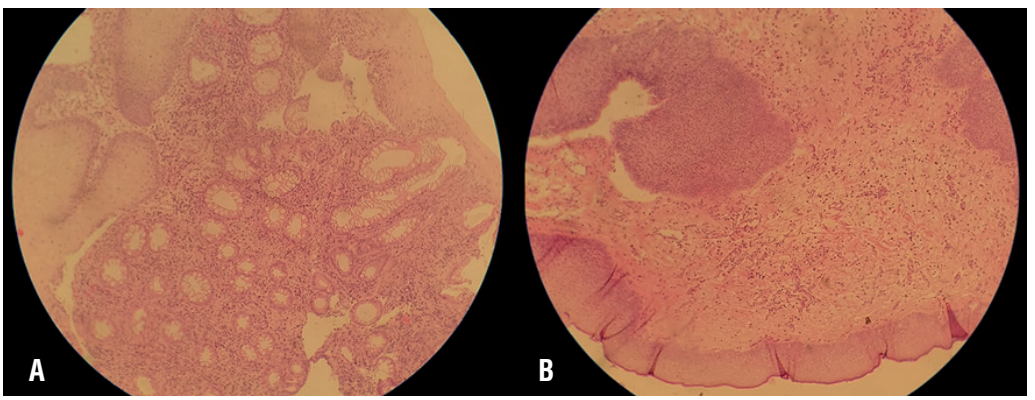


Figure 4 - Histological evaluation of the biopsies taken from patients with LDPE (A) and PVdC (B) wrap with no malignancy or pathological changes (×40).



from the early surgical intervention. By this technique, we can conclude that reducing the size and number of polyps before the operation may prevent further malignant potential of cystitis glandularis in polyps that are excised at secondary and delayed primary closure.

In order to reduce probable postoperative complications and achieve an acceptable continence, a careful and useful preoperative management of polyps are attainable in these selected patients and may lead to better postoperative success. Due to the fact that neonates and infants are more susceptible to preoperative complications compared with older children, we tried to evaluate the difference of PVdC and LDPE wraps in the preoperative management of polyps in patients with BEEC.

PVdC is a synthetic resin which is produced by vinylidene chloride polymerization and is a high barrier against water, aromas, oxygen, mold, bacteria, and insects. PVdC is mainly used in impermeable and flexible food wraps. PVdC is insoluble in oil and organic solvents; moreover, it is resistant to alkalizes and acids. It should be also mentioned that PVdC can release acid gas (HCl) in special conditions (exposure to gamma radiation and temperature above 125°C) (14). Copolymers of vinylidene chloride and other monomers have become popular in recent years as alternatives of PVdC with less environmental concerns. However, the amount of cling provided by LDPE plastic wraps is not as much as that PVdC plastic wraps (6, 15-17). In spite of the fact that PVdC may not be environmentally suitable due to its harmful effect after being exposed to gamma radiation or high temperatures, it may be a good choice for the coverage of the exposed bladder in patients with BEEC. On the other hand, its harmful effects do not appear in clinical conditions in which the wrap is used in room temperature and the child is not exposed to gamma radiation. These high-barrier wraps are commercially available with a low price ranging $ 2-4 (18). The results of our study revealed no harmful effects to skin by the application of PVdC while the bladders that were covered with LDPE showed mild skin allergy.

It has been confirmed that success after initial bladder closure in patients with BEEC can develop satisfactory bladder capacity and continence, reduce overall costs, and decrease the incidence of inflammation and fibrosis of the bladder (19-21). Considering the fact that the size and numbers of polyps decreased and operation could be performed earlier, more satisfactory postoperative results may be achieved in these patients. However, more evaluations in larger cohorts are needed to prove this theory. Improvement in quality of life, better postoperative managements, and decrease in the number of surgical procedures, costs, and patients discomfort are among the benefits of the current survey. Although the failure of primary closure

is too complex and multifactorial, the size and number of polyps presented prior to operation can be considered as an etiology. It has been mentioned that increased inflammatory injury can occur as the result of repeat closure (6). However, by the application of a proper wrap before the operation, the number of surgeries and consequent inflammatory injury may be reduced.

To our knowledge, the current study is unique in that preoperative management of polyps in BEEC cases has not been evaluated previously. The current study has some imitations. Due to the small number of patients, statistical significance was not reached. Moreover, the postoperative outcomes of these patients were not evaluated to detect any significant difference in achieving an uneventful postoperative period. We speculated that the application of these wraps may improve the overall success of the surgical intervention and eventual continence postoperatively. However, more studies are necessary to investigate the bladder capacity, bladder growth, and histopathological finding of these patients in a large group of selected patients.

CONCLUSIONS

On the basis of the current data and our experience before and after the application of these non-adherent films, we tend to recommend a type of PVdC wrap (high-barrier) which may be preferable in preventing any further possible infection and allergic reactions of the exposed bladder region and reducing the size and number of polyps compared to other frequently used wraps.

ABBREVIATIONS

BEEC = bladder exstrophy epispadias complex
PVdC = polyvinylidene chloride
LDPE = low density polyethylene

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CONFLICT OF INTEREST

None declared.

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Evaluation of apoptosis indexes in currently used oral alpha-blockers in prostate: a pilot study

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ABSTRACT

Objectives: Apoptosis effect of oral alpha-blockers is known in the prostate. Apoptosis index of silodosin has not been proved, yet. Aims are to present apoptosis index of silodosin in prostate and to compare this with other currently used alpha-blocker's apoptosis indexes together with their clinical effects.

Materials and Methods: Benign prostatic hyperplasia (BPH) patients were enrolled among those admitted to urology outpatient clinic between June 2014 and June 2015. Study groups were created according to randomly prescribed oral alpha-blocker drugs as silodosin 8mg (Group 1; n=24), tamsulosin 0.4mg (Group 2; n=30), alfuzosin 10mg (Group 3; n=25), doxazosin 8mg (Group 4; n=22), terazosin 5mg (Group 5; n=15). Patients who refused to use any alpha-blocker drug were included into Group 6 as control group (n=16). We investigated apoptosis indexes of the drugs in prostatic tissues that were taken from patient's surgery (transurethral resection of prostate) and/or prostate biopsies. Immunochemical dyeing, light microscope, and Image Processing and Analysis in Java were used for evaluations. Statistical significant p was $p<0.05$.

Results: There were 132 patients with mean follow-up of 4.2 ± 2.1 months. Pathologist researched randomly selected 10 areas in each microscope set. Group 1 showed statistical significant difference apoptosis index in immunochemical TUNEL dyeing and image software ($p<0.001$). Moreover, we determined superior significant development in parameters as uroflowmetry, quality of life scores, and international prostate symptom score in Group 1.

Conclusions: Silodosin has higher apoptosis effect than other alpha-blockers in prostate. Thus, clinic improvement with silodosin was proved by histologic studies. Besides, static factor of BPH may be overcome with creating apoptosis.

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Prostate; Prostatic Hyperplasia; 5-alpha Reductase Inhibitors

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most frequent diseases in aging men (1). BPH contains static and dynamic factors and these contribute to urinary obstruction during its process (1). Alpha-blocker drugs are initially used as medical treatment of choice (2). Besides, the exact mechanisms of these drugs are still under clinical and laboratory investigations. Nevertheless, selec-

tive alpha-receptor blockers are currently used for symptomatic BPH (3). These drugs certainly blockade alpha-receptors in prostatic tissue. Thus, clinical symptoms of BPH can be reduced. Moreover, these are mostly related with dynamic obstruction of BPH. Previous studies pointed some apoptosis, which is a programmed cell death, in prostate by some of these drugs (4). Additionally, it could not have been proved that the apoptotic action of alpha-blockers could contribute to their clinical efficiency in BPH (5). According to our best knowledge, published studies on apoptotic effect of alpha-blockers did not investigate silodosin and its clinical reflection due to apoptosis.

In the present study, we aimed to compare apoptosis index of currently used oral alpha-blockers in prostate. Furthermore, we evaluated the clinical reflection of apoptotic indexes of silodosin and other alpha-blockers in prostate, as the first in published literature. Our hypothesis was high selectivity of alpha-blockers can lead to more apoptosis in prostate.

MATERIALS AND METHODS

Study Design

This study was a retrospective view of prospective collected data and open-labelled and non-randomized clinical investigation. All procedures performed in the present study involving human participants were in accordance with the ethical standards of our institutional research committee and with the 2008 Helsinki declaration and/or its later amendments or comparable ethical standards. Additionally, all patients understood the treatment and aim of the study. The written informed consents were obtained. Ethical committee of our institute approved the study and numbered as "14115".

Exclusion criteria included the use of 5-alpha reductase inhibitors and/or phytotherapy, presence of prostate cancer, any prostatitis, previous prostate surgery or other minimally invasive interventions for prostate, senile dementia, urinary dysfunction such as neurogenic bladder, post voiding residual urine (PVR) >100mL, bladder neck sclerosis, Alzheimer's disease, urethral stricture, bladder stone, urinary tract infection, alpha-blockers drug hypersensitivity, hepatic and/or renal impairment, severe cardiovascular disease and any other cancer. Patients with prostate specific antigen (PSA) >4ng/dL with/without rigid nodule in digital rectal examination (DRE) were excluded for further investigations with prostate biopsy.

BPH patients admitted to urology outpatient clinic between, June 2014 and June 2015, were enrolled. Data was recorded prospectively and was evaluated retrospectively.

Patient data

Demographic data included age, comorbidities, previous operation history, physical examination including DRE, blood analysis including prostate specific antigen (PSA), liver and kidney functions (creatinine, blood-urea-nitrogen), urinalysis, uroflowmetry (UFM) (Solar Uroflow, Medical Measurement Systems, Inc. Dover, NH 03820, USA) and determination of PVR (The BioCon 500, Medline LA, CA 90245, USA), International prostate symptom score (IPSS), Quality of life (QoL) index, transrectal ultrasonography of prostate (TRUS) with 7.5Mhz probe (Sonoline SL 450, Siemens AG, Erlangen, Germany) were performed.

The groups were created according to randomly prescribed oral alpha-blockers: silodosin 8mg (Group 1; n=24), tamsulosin 0.4mg (Group 2; n=30), alfuzosin 10mg (Group 3; n=25), doxazosin 8mg (Group 4; n=22), terazosin 5mg (Group 5; n= 15). The control group (Group 6; n=16) consisted of BPH patients who had not used any alpha-blocker/or did not want to use any drug for BPH; transurethral resection of prostate (TURP) was performed. The prostatic tissues were taken from TURP operations and/or prostatic biopsies. The biopsies were performed in patients who were in clinical follow-up and had suspicious prostate nodule in DRE and/or suspicious change in PSA level.

The IPSS and UFM, QoL indexes were recorded before drug administration, and after 1st, 6th, and 12th month of drug administration.

Histopathology

The experienced pathologist evaluated all tissues and TUNEL immunochemistry was used for determining apoptosis indexes in prostatic tissues

that were removed and immediately half of them were fixed in 10% neutral buffered formalin. Then, dehydration in the graded ethanol series and clearing with xylene, the sample material was placed into paraffin. Immediately after, 4µm-thick sections were stained with Haematoxylin-Eosin (HE).

Detection of apoptotic cells

The terminal deoxynucleotidyl transferase-mediated dUTP nick end-labelling (TUNEL) was used to determine apoptotic cells by stain using a commercial ready-to-use kit (In Situ Cell Death Detection Kit, POD, Roche, Mannheim, Germany). All steps of the process were performed according to instructions of manufacturer. Shortly, 4µm paraffin sections were prepared on silanized slides. Then, deparaffinization and rehydration were performed and slides were digested with proteinase K (20µg/mL, 30 min.) and quenched with 3% hydrogen peroxide in methanol. The incubation was performed in a humidified chamber in 200µL of TUNEL (TdT and label solution) at 37°C for 60 min. and with POD converter at 37°C for 30 min. The sections were then handled with DAP for 5 min., washed with PBS and counterstained with Mayer's haematoxylin.

Tissue sections were evaluated by high power light microscopic examination Olympus Bx52 with DP72 camera system. All immunohistochemically staining were estimated with an image processing system (Olympus, DP2-BSW). Each TUNEL stain specimen was examined according to 10 randomly selected areas of approximately X40 objectives.

The scores were derived semi-quantitatively using light microscopy on the preparations from each slide and were reported as follows: none: –, mild: +, moderate: ++, severe: +++, and very strong: ++++. Additionally, we used quantification program as Image Processing and Analysis in Java (ImageJ 1.51j8, NIH, USA) for analysing the apoptosis indexes in images. All results were double-checked.

Statistical analyses

The Statistical Package for the Social Sciences (SPSS) V 16.0 was used for statistical analyses. One-way ANOVA was used for comparing mean data among groups. The significant p was accepted as $p<0.05$.

RESULTS

We evaluated 132BPH patients with mean follow-up of 4.2 ± 2.1 months. Demographic data was comparable among groups (Table-1). The mean baseline maximum urine flow rate in uroflowmetry (Qmax) in Group-6 was 11.6 ± 5.1 and we did not include this into statistical analyses. However, the baseline mean Qmax was comparable in all groups when we included data of Group-6 in analyses. The alteration in Qmax is presented in Table-2. There was significant development in Qmax with silodosin (Group-1) during follow-up. This rate was kept during up to 1 year. We did not include Group-6 into Table-2 because we wanted to compare just clinical effects of alpha-blockers.

Additionally, the IPSS scores were significant decreased with silodosin (Group-1) then other groups in 1st, 6th, and 12th months of follow-up (respectively; 0.04, 0.04, 0.003). The QoL scores were significant developed with Silodosin than other drugs. The most significant difference was obtained in the 12th month of treatment (P=0.003). We did not include Group-6 in comparison of IPSS and QoL since we were comparing the clinical effects of alpha-blockers.

In pathology examination, 10 random areas were evaluated in each microscope slide. However, the apoptosis index of Group 3 and 4 was very close to apoptosis index of Group-1. Nevertheless, in statistical analyses Group-1 had significant apoptosis index (P<0.001) (Table-3). The HE stained tissues showed some cystic degenerated cells and reproduction of these into tubule lumen. The most inflammation was observed in Group-6 and the lowest level of inflammation was obtained in Group-2 (Figure-1) (Table-3).

The immunohistochemically TUNEL staining showed significant differences for apoptosis among Groups (Figure-2). The numbers that were got from Image J Software were also added into Table-3.

The most seen side effect of alpha-blockers was dizziness. However, 3 patients reported anejaculation with silodosin and 1 patient reported this

Table 1 - Demographic data of groups.

Parameter	Group 1 (n=24)	Group 2 (n=30)	Group 3 (n=25)	Group 4 (n=22)	Group 5 (n=15)	Group 6 (n=16)	P value
Age (years)	68.1±8.5	70.7±8.5	68.1±8.4	70.2±8.8	73.3±8.2	67.7±9.5	0.4
PSA (ng/dL)	3.2±1.6	2.8±1.7	2.9±1.8	3.1±1.9	2.9±1.7	3.1±2.2	0.9
Serum creatinine (mg/dL)	1.4±2.1	1.3±1.6	1.2±1.1	0.9±0.3	1.1±0.6	1.4±0.8	0.5
Prostate volume (mL)	37.4±4.7	38.2±3.8	36.1±4.1	35.2±3.7	37.2±4.3	36.1±5.1	0.1

PSA = Prostate specific antigen

Table 2 - Comparison of clinical findings on uroflowmetry in Groups.

Parameter	Group 1 (n=24)	Group 2 (n=30)	Group 3 (n=25)	Group 4 (n=22)	Group 5 (n=15)	P value
Mean Qmax at baseline	11.2±3.8	12.4±4.1	12.1±3.5	12.9±3.3	11.8±2.7	0.57
Mean Qmax at the 1st month	18.8±8.1	16.2±7.7	14.1±7.2	13.4±4.9	13.5±6.1	0.04*
Mean Qmax at the 6th month	18.9±8.8	16±7	14.3±6.8	13.4±4.9	13.2±6.3	0.04*
Mean Qmax at the 12th month	18.6±9.2	16.4±8.1	14±5.7	13.1±4.7	13±5.9	0.03*

Qmax = Maximum flow rate in uroflowmetry (mL/sec)

* Statistical significant p value.

Table 3 - Comparison of apoptosis indexes of Groups.

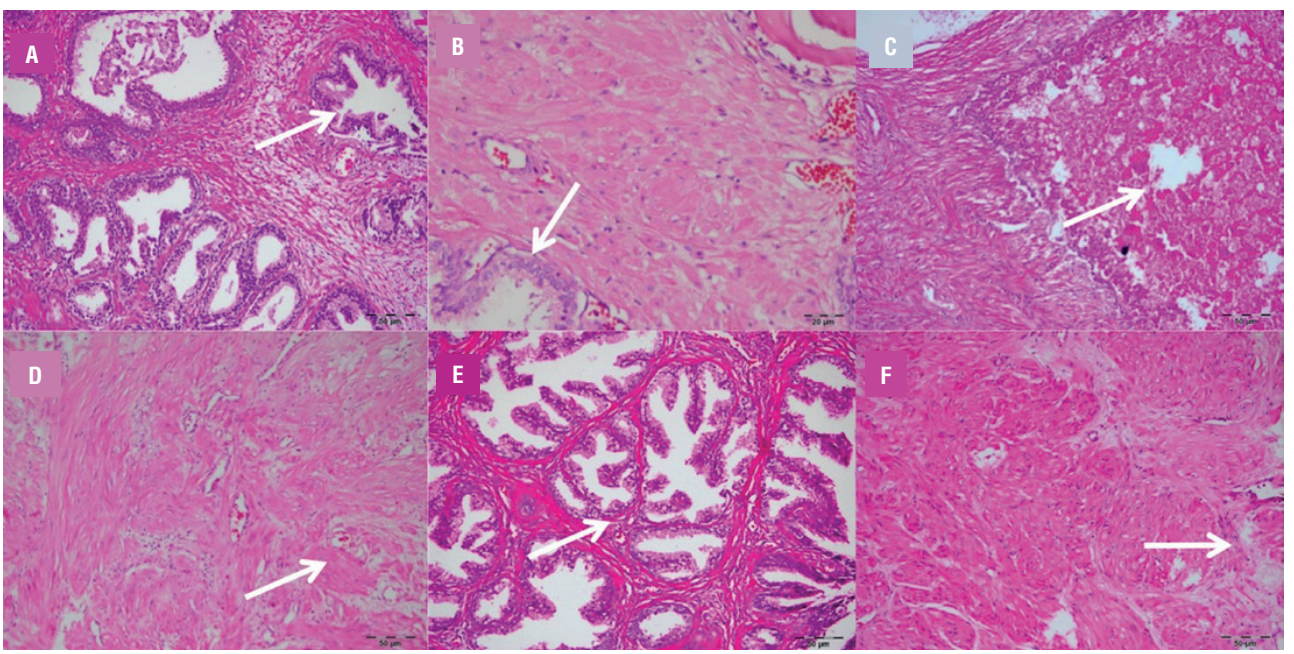
Parameters	Group 1 (silodosin) n=24	Grouop 2 (Tamsulosin) n=30	Group 3 (Alfuzosin) n=25	Group 4 (Doxazosin) n=22	Group 5 (Terazosin) n=15	Group 6 (Controls) n=16	P Value
Apoptosis index in glandular epithelium	++++ (227**)	++ (161**)	+++ (182**)	+++ (184**)	+++ (188**)	+ (119**)	P<0.001*
Apoptosis index in myocytes	++++	++	+	+++	+++	+	P<0.001*
Inflammatory cells	+++	++	+	+++	+++	+	N.A.
Apoptosis index in vascular endothelial cells	++++	++	+	+++	++	+	P<0.001*
Apoptosis index in stroma	++++	++	++	+++	+++	+	P<0.001*

* Statistical significant P value.

** The numbers were recorded from Image Processing and Analysis in Java software by evaluation of Figure 2.

N.A = Not assessed

Figure 1 - The Haematoxylin-Eosin dyed view of groups. A) The arrow shows glandular reproduction and inflammation in cells of Group-1, B) The more decreased level of inflammation was observed in Group-2 with Haematoxylin-Eosin dying. C) The arrow shows glandular hyperplasia in Group-3, D) The arrow shows glandular hyperplasia with mild amyloid deposition in Group-4, E) The arrow shows glandular hyperplasia with intertubular of lymphocytes and macrophages were creating inflammation in Group-5, F) The most inflammation was observed in Group-6.



Scale bars=20μm for B. Scale bars=50μm for A, C, D, E, and F.

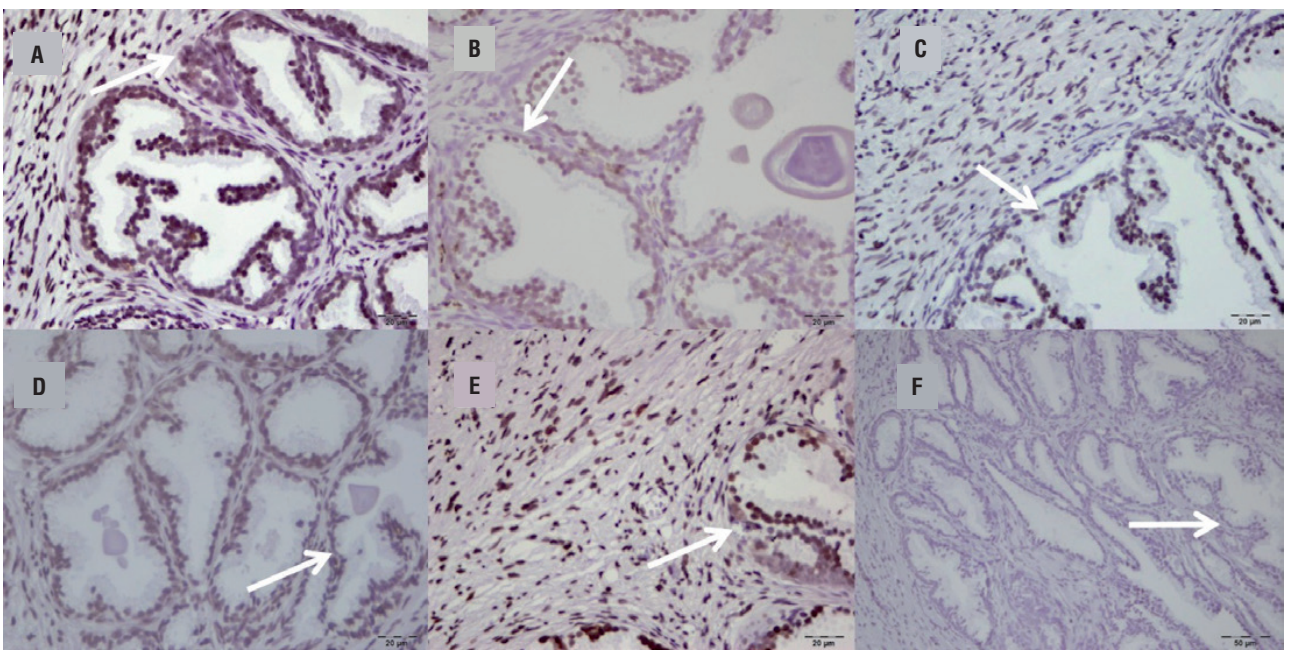
side effect with tamsulosin. No patient withdrawal the treatment.

DISCUSSION

Apoptosis is the programmed cell death as part of cell's lifecycle (6). It can be induced and can be increased by drugs. The hyperplasia index occurs much more than apoptosis index in BPH. Up till now, apoptotic effects of terazosin (7), Doxazosin (7), alfuzosin (8), and tamsulosin (9) were published in the literature. Increased apoptosis may decrease prostate volume and static factor in BPH can be overcome. Thus, the possible clinical efficacy of these drugs can be beneficial for symptomatic BPH. However, according to our best knowledge, there has not been published any study on clinical effects of these processes (4, 5, 10). Nevertheless, oral alpha-blockers can increase apoptosis in prostatic tissue whether in glands and/or smooth muscles. In the present study, we compared apoptosis indexes of actually used oral alpha-blockers. Additionally, we evaluated clinical effects of apoptotic indexes of these drugs. Silodosin was the most effective alpha-blocker and had the most apoptotic index in prostate. To our best knowledge, this is the first study that apoptosis of silodosin on prostate was showed and was compared with other alpha-blockers. Moreover, clinical effects of apoptosis were presented.

We found significant higher apoptosis index could be obtained with silodosin then other drugs. Moreover, there was an interesting significant clinical reflection in favour of silodosin (11). Yoshida et al. reported that silodosin was more significantly effective then tamsulosin on voiding as well as on uroflowmetric parameters in short-term (12). Our findings were parallel to them. Silodosin provided significant increase in Qmax and decrease in IPSS than other alpha-blockers. We think that this may be related with silodosin's highly selective effect on alfa-1a receptors (11, 12).

Figure 2 - Apoptosis indexes in immunohistochemistry with TUNEL dyeing. A) The most apoptosis was observed in Group-1 (Arrow shows apoptotic cells), B) There was mild apoptosis in Group-2 (Arrow), C) Apoptotic gland in Group-3 (Arrow), D) Apoptotic glands around tissue in Group-4 (Arrow), E) Apoptosis in Group-5 (Arrow), F) The decreased level of apoptosis in Group-6 (Control) (Arrow).



Scale bars=20µm for A-E. Scale bars=50µm for F.

Miyakita et al. reported significant improvement of QoL with silodosin (13). We agree with them and there was significant development in QoL with silodosin than other alpha-blockers. We strongly think that this is another reflection of highly selective blockade activity of silodosin on alpha-1A receptors (14). High QoL parameters can be obtained with reduced nocturnal urination, relieved urination, and effective emptying bladder. In our study, reduced nocturia was the most effective developed symptom that could contribute to improve QoL parameters.

On the other hand, Chlosta et al. reported apoptosis with alpha-blockers in prostate and stated that there was no reflection of these on BPH's clinical symptoms (5). We do not agree with them. There were significant clinical improvements with silodosin in terms of decreased IPSS and increased Qmax with developed QoL, in the present study. Creta et al. reported improved urodynamic parameters with silodosin (15). Our findings supported their report. This may be another proof of overcoming static factor of BPH by using silodosin. However, there is need of more studies on urodynamic outcomes of silodosin usage.

Partin et al. reported apoptosis with doxazosin mediated transforming factor beta-1 (10). Garcia-Cazare et al. revealed induced mitochondrial p53 translocation by alpha-blockers (6). Unfortunately, we did not study on molecular mechanism of Silodosin's effectivity. This may be subject of our future study.

There were some side effects related with alpha-blockers. Dizziness was the most seen side effect. It healed in course of therapy spontaneously. It was very well known that alpha blockers can cause dizziness in terms of its pharmacological mechanism (16). However, there was no dizziness with silodosin. Anejaculation was the other most seen side effect in 3 patients using silodosin and in 1 patient using tamsulosin. Anejaculation did not cause withdrawal of silodosin as well as of tamsulosin. The possible mechanism was discussed before (17). On the other hand, Moon et

al. concluded safety of Silodosin in a recent study (18). We agree with Moon et al. (18) and the safety the drug was proven in the present study.

We have some limitations in the present study. At first, it was an open labelled non-randomized retrospective pattern study. Low numbers and unbalanced specimen distribution of patients in groups are one of the other limitations. However, we showed apoptosis in prostatic tissue, we did not study on accurate molecular mechanism of alpha-blockers in prostate. Furthermore, we did not detect for prostate volume of patients because some of them underwent TURP. Besides, we did not compare operational data according to used alpha--blockers. Nonetheless, we focused on apoptosis indexes and clinical effects of alpha-blockers. Lastly, Group-6 was not a real control group, however, we included patients suffering from severe lower urinary tract symptoms (LUTS) into that group. At that time, measurement of the obstruction due to LUTS come into question and normally it brings to use urodynamics. We did not perform any urodynamics to LUTS patients in the groups.

The goals of the present study are the highest apoptotic effects of silodosin were showed in histological and immunochemistry staining with its clinical reflection in terms of improved IPSS, QoL, and Qmax. Additionally we focused on effects of silodosin in the present study. This study is the first in the literature that clinically analyse silodosin's histologic effects. All these are unique in the literature.

CONCLUSIONS

Silodosin has the highest levels of apoptosis index in the prostate among currently used alpha-blockers during medical treatment of BPH. Urination symptoms can be reduced and high QoL index can be gained with silodosin. Thus, static factor during BPH can be reduced with silodosin. There is need of more studies with molecular investigations and clinical urodynamic examinations on this issue with high number of patients.

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CONFLICT OF INTEREST

None declared.

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The role of fetal-maternal microchimerism as a natural-born healer in integrity improvement of maternal damaged kidney

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ABSTRACT

Purpose: To identify the fetal stem cell (FSC) response to maternal renal injury with emphasis on renal integrity improvement and Y chromosome detection in damaged maternal kidney.

Materials and Methods: Eight non-green fluorescent protein (GFP) transgenic Sprague-Dawley rats were mated with GFP-positive transgenic male rats. Renal damage was induced on the right kidney at gestational day 11. The same procedure was performed in eight non-pregnant rats as control group. Three months after delivery, right nephrectomy was performed in order to evaluate the injured kidney. The fresh perfused kidneys were stained with anti-GFP antibody. Polymerase chain reaction (PCR) assay was also performed for the Y chromosome detection. Cell culture was performed to detect the GFP-positive cells. Technetium-99m-DMSA renal scan and single-photon emission computed tomography (SPECT) were performed after renal damage induction and 3 months later to evaluate the improvement of renal integrity.

Results: The presence of FSCs was confirmed by immune histochemical staining as well as immunofluorescent imaging of the damaged part. Gradient PCR of female rat purified DNA demonstrated the presence of Y-chromosome in the damaged maternal kidney. Moreover, the culture of kidney cells showed GPF- positive cells by immunofluorescence microscopy. The acute renal scar was repaired and the integrity of damaged kidney reached to near normal levels in experimental group as shown in DMSA scan. However, no significant improvement was observed in control group.

Conclusion: FSC seems to be the main mechanism in repairing of the maternal renal injury during pregnancy as indicated by Y chromosome and GFP-positive cells in the sub-cultured medium.

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INTRODUCTION

Fetal maternal cell trafficking (FMCT) can be defined as the presence of cells originating from genetically distinct individual without evidence of immunological response. FMCT is considered to be the trafficking of semi-allogenic fetal cells into the maternal circulation that may culminate in a mixtue of both maternal and fetal cells in maternal tissue during and after pregnancy. Several studies have demonstrated the persistence of FMCT in the $CD34^+$ population for more than 30 years after delivery (1). Male cell markers have been applied in most studies

because of its simplicity in identification of FMCT. In addition, FMCT is derived from both male and female fetus (2). Immune tolerance of the mother to the fetus and vice versa also appears to develop by this phenomenon (3). Migration, engraftment and differentiation of fetal stem cells (FSCs) to several maternal tissues during the pregnancy may happen, especially in damaged host organ (4-6). FSCs may have a crucial role in healing maternal damaged organs during the pregnancy by passing through the placenta and entering the maternal blood circulation. FSCs have also the ability to migrate to sites of the affected maternal organs, differentiate, and proliferate locally.

However, methods to determine the role of fetal progenitor cells in treating damaged organs during the pregnancy are still laborious. The accretion of FSCs in the local damaged organs may be due to the consequence of the disease; or caused by the response to tissue injury. Furthermore, it has been considered that FSCs have the ability to gain tissue specific markers as they migrate to the environment of damaged maternal organ (74). To date, the role of FSCs in functional improvement of the damaged organ has not been well evaluated.

In the current animal model, we used transgenic male rats expressing green fluorescent protein (GFP) in order to achieve the best sensitivity for better detection of FSCs in the maternal damaged kidney. The aim of the current study was to investigate the multilineage capacity of FSCs in repairing of maternal injured kidney as well as improving its functional capacity in a rat model of FMCT by detecting Y-chromosome and GFP-positive cells in the damaged part of maternal kidney.

MATERIALS AND METHODS

Animal model of FMCT and the subsequent induction of renal damage

The local ethics committee approved the experimental protocol. The principles of laboratory animal care (NIH publication no. 85-23, revised 1985) were respected for animal treatment.

Eight non-GFP female Sprague-Dawley rats weighting 220-310g were mated with GFP-positive male rats. All rats were maintained in standard single cages on a 12h darkness/12h light cycle with the best access to standard feed and water ad libitum in our laboratory. The rats were examined at 8h interval for detection of vaginal plague. The identification of vaginal plague was considered as gestational day 0 (GD0). Afterwards, female rats were kept in separate cages with consummative diet.

Renal mass ablation by specially designed diathermy or electrocautery probe has been employed by several studies (8-11). At GD 11, the rats were anesthetized by administering intraperitoneal Ketamine (40mg/kg) and Xylazine (4mg/kg) and the right lateral flank was shaved and swabbed with a solution of 0.5% chlorhexidine in 70% alcohol (Hibitane®). For right kidney exposure, a lateral incision was made before separating the kidney from the adrenal gland and perirenal fat. Then, the renal damage (focal burning) was performed on the lateral upper pole of the right kidney. The degree of burning could be precisely controlled by the period of contact with the kidney. In summary, the right upper renal pole was cauterized for a period of 4 seconds by the application of conventional cautery to avoid the incidence of necrosis as an irreversible renal injury. The maintenance of anesthesia was obtained by the injection of 0.75mg/kg Ketamine with 20 minutes intervals. The rats were then kept in specific cages under intensive care for terminating the gestational period. The same procedure was also performed in eight non-pregnant rats as control group to compare the role of FSCs in repair of damaged maternal kidney.

Immunohistochemistry and immunofluorescence of fixed frozen samples

After 3 months of delivery, the rats underwent a nephrectomy surgery by the same surgeon in order to dissect the injured kidney. The kidneys were perfused with phosphate buffered saline to remove the red blood cells and were stained with anti-GFP antibody for identification of the FSCs in the non-GFP maternal damaged kidney. Anti-GFP antibody was purchased from Dako® (Trappes, France). In summary, deparaffinized and rehydrated samples underwent antigen retrieval by the application of Tris/EDTA buffer (pH=9.0) and a vegetable steamer. Endogenous peroxidase was blocked with horseradish peroxidase (HRP). In the

next step, slides were blocked in 10% normal serum with 1% bovine serum albumin (BSA) in TBS for 2h, after being washed in Tris buffered saline (TBS) plus 0.025% Triton X-100. Appropriate dilution of antibodies was applied for overnight incubation of the slides.

The fresh frozen samples were also analyzed by immunofluorescent microscopy to verify the cell trafficking of GFP-positive cells in the kidney of non-GFP rat. Other organs, including liver and lung were also analyzed by immunofluorescent microscopy in order to detect homing of GFP-positive cells in undamaged tissues.

PCR

For PCR of the Y chromosome which was performed on genomic DNA, upper pole renal DNA was extracted using the QIAamp® DNA kit (Qiagen AG, Basel, Switzerland) after nephrectomy of the damaged kidneys. The ubiquitous β-globin gene was amplified by PCR for the purpose of controlling the quality of extracted DNA and the lack of PCR inhibitors (12). Y chromosome DNA amplification was performed by the application of 1 microgram of extracted DNA by means of a single PCR assay with the primer set CNX43-F (5'-TTC CTT TGA CTT CAG CCT CC-3'), CNX43-R (5'-GTG TTA CAG CGA AAG GCA G-3'), KH-1F (5'-GAG AGA GGC ACA AGT TGG C-3'), and KH-1R (5'-GCC TCC TGG AAA AAG GGC C-3'). The PCR steps included denaturation at 94°C for 4 minutes, 38 cycles of amplification, and elongation at 72°C for 10 minutes. After electrophoresis with a 1.5% agarose gel at different temperatures, ethidium bromide staining was utilized to observe the results under UV trans-illumination.

Cell Culture

After dissection of the damaged kidney in sterile condition, the upper pole of the kidney was cut into 5- to 10mm-thick coronal slices. The fragments were washed in chilled basal medium. The fragments from the damaged section were minced into 1- to 2mm pieces with crossed blades. Tissue fragments (an approximate amount of 5mL) were transferred to a tube containing 20mL of warm collagenase-trypsin solution. The tissue was incubated in an orbital shaker with gentle agitation within an incubator at 37°C for 1h. Subsequently, 20mL of basal medium containing 0.05mg/mL DNase was added and the supernatant was gathered at 20-min intervals with gentle trituration. The collected supernatant was diluted with an equivalent volume of complete culture medium, dispensed into aliquots in 50mL tubes, and centrifuged at 100g for 15 min. Then, each pellet was resuspend in 45mL of complete medium and seeded 15 into one 75cm^2 flask. The sub-cultured cells were analyzed by immunofluorescence microscopy in order to detect the GFP-positive FSCs.

Technetium-99m DMSA renal scan *and single-photon emission computed tomography (SPECT)*

After induction of renal damage and three months after delivery in experimental group and three months after renal damage in control group, Technetium-99m-DMSA solution was injected into the tail vein of rats to determine the differential renal function of the damaged kidney in four rats of each control and experimental groups. The mean renal function was obtained in both groups. As DMSA solution needs approximately 4-6 hours to travel around the blood stream to reach the kidneys, anesthesia was maintained during this period. The progress of the DMSA solution through the kidneys was traced with a single-head rotating camera. For SPECT, an Elscint® SP-1 computer was applied to produce images representing slices through the kidneys in different planes in four rats of each control and experimental groups. The images obtained by SPECT are functional in nature rather than being purely anatomical.

RESULTS

All rats survived the whole period of our study. The presence of FMCT in renal papilla and tubular epithelial cells was confirmed by immunohistochemistry staining and immunofluorescence analysis of the damaged kidneys. These results indicated that fetal cells were present in

the maternal peripheral circulation and they also contributed to the repairing process of maternal kidney by migrating to the damaged parts for further differentiation. As depicted in Figure-1 (A) GFP positive cells formed both tubular and interstitial lesions. However, no detectable focal aggregation of GFP-positive cells was found in immunofluorescent microscopy of lung and liver as samples of undamaged organs.

The presence of Y-chromosome in the damaged maternal kidney was obviously proved by the gradient PCR of female rat purified DNA. Regarding the fact that the exact temperature for PCR of this specific primer was unknown, gradient PCR method was applied for a purified DNA sample at different temperatures. Results of the gradient PCR showed that the most appropriate temperature for this specimen was 54°C. Gradient PCR at 49°C was applied in order to reassure the specific and non-specific binding of the primer.

The sub-cultured cells from the damaged part of the non-GFP kidney were viewed with immunofluorescent microscopy. The GFP-positive renal cells were observed in company with undamaged maternal renal cells (Figure-1B).

led decreased renal function in the right kidney in which the damage was induced (41%±0.9% versus 59%±0.8%). However, similar uptake in both damaged (right) and normal kidneys (left) with uniform distribution pattern of renal activity was obtained 3 months after delivery (49%±0.7% versus 51%±0.4%). The results of DMSA scan in control group revealed no significant improvement in function of right kidney (mean±SD) after 3 months of renal damage induction (40%±0.3% versus 60%±0.7% after renal damage and 42%±0.8% versus 58%±0.6% ,3 months postoperatively). DMSA scan of pregnant and non-pregnant rats confirmed the role of FSCs in repairing the damaged part of the kidney (Table-1). The split renal function described in the DMSA scan was from average data of the groups (Figures 1-C-F). The results of DMSA scan were compatible with the outcomes obtained from SPECT. SPECT of control group showed renal damage in several continuous sections while satisfactory results without any detectable renal impairment were obtained in none of the sections in experimental group 3 months after operation (Figure-2).

Table 1 - Comparing the renal function after renal damage induction and 3 months postoperatively in pregnant (experimental group) and non-pregnant (control group) rats.

		Experimental group		Control group		p value
		Right kidney	Left kidney	Right kidney	Left kidney	
Mean ± SD DMSA Renal scan (%)	After renal damage induction	41±0.9	59 ± 0.8	40 ± 0.3	60 ± 0.7	
	3 months after renal damage	49±0.7	51 ± 0.4	42 ± 0.8	58 ± 0.6	0.02

Renal imaging was performed by the application of Technetium-99m-DMSA solution the high percentage of which in the renal cortex results in the high gamma flow. Each of the static scintiphotos was obtained by the application of a high-resolution collimator 1 hour after administration of Technetium-99m-DMSA solution. The result of DMSA scan after induction of renal damage in experimental group revea-

DISCUSSION

The current experimental study provided an overview about the role of FSCs in healing maternal renal damage during pregnancy where the GFP is set as the marker of fetal-origin cells in the maternal damaged part of kidney. The focus of the current study was on determining the role of FCSs in maternal renal function improvement.

Figure 1 - (A) Immunofluorescence of damaged part of maternal non-GFP kidney. Arrow a shows the damaged part of maternal kidney which is covered by GFP-positive FSCs. Arrow b shows the undamaged non-GFP maternal kidney; (B) Fetal GFP-positive cells in company with maternal non-GFP renal cells after culture of the damaged part from the upper pole. Technetium-99m-DMSA scan of pregnant rats (experimental group); (C) differential renal function after induction of renal damage confirmed decreased renal function on right kidney; (D) Renal function was similar in both kidneys three months postoperatively. Technetium-99m-DMSA scan of non-pregnant rats (control group); (E) differential renal function after induction of renal damage confirmed decreased renal function on right kidney; (F) Renal function did not improve significantly three months after renal damage induction

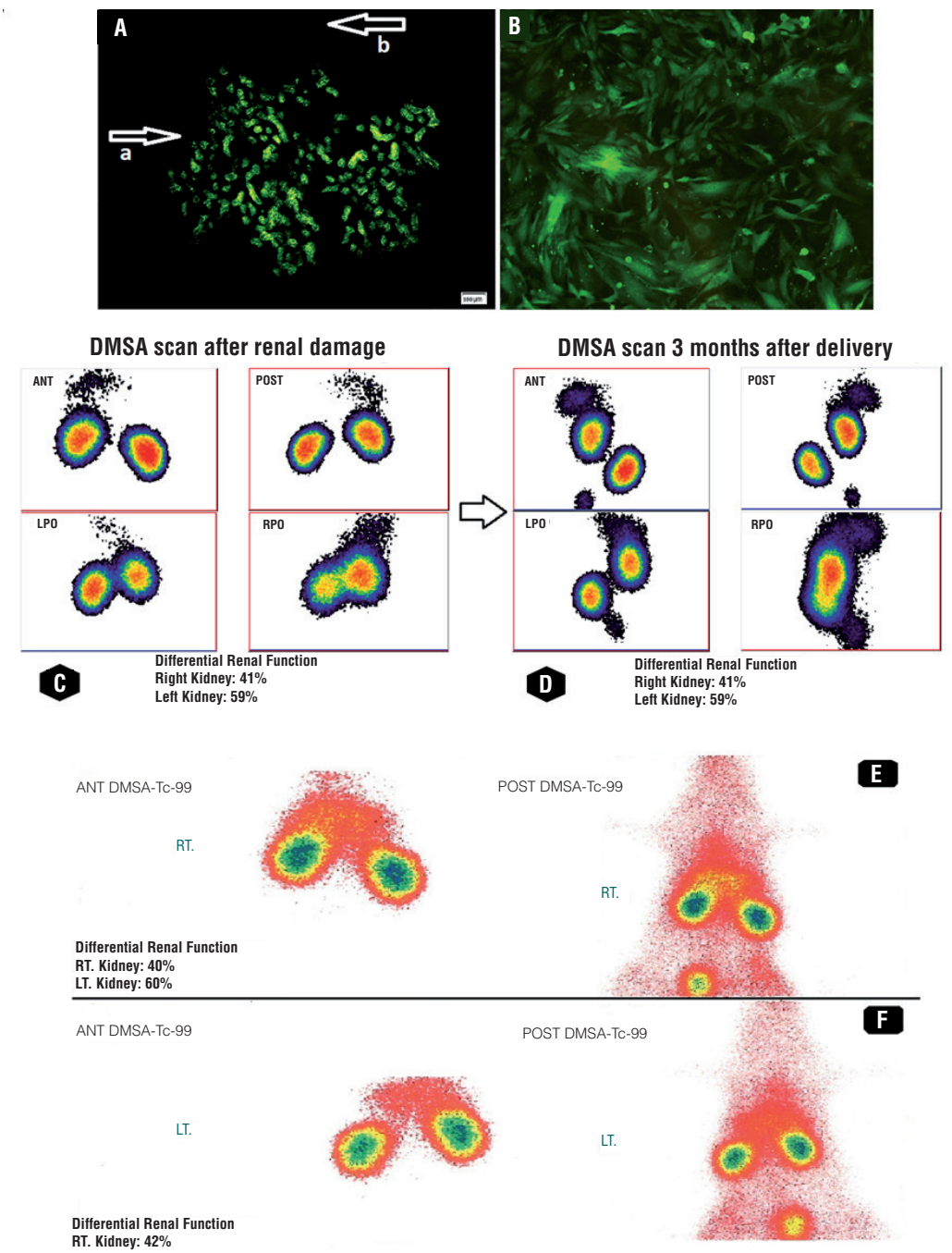
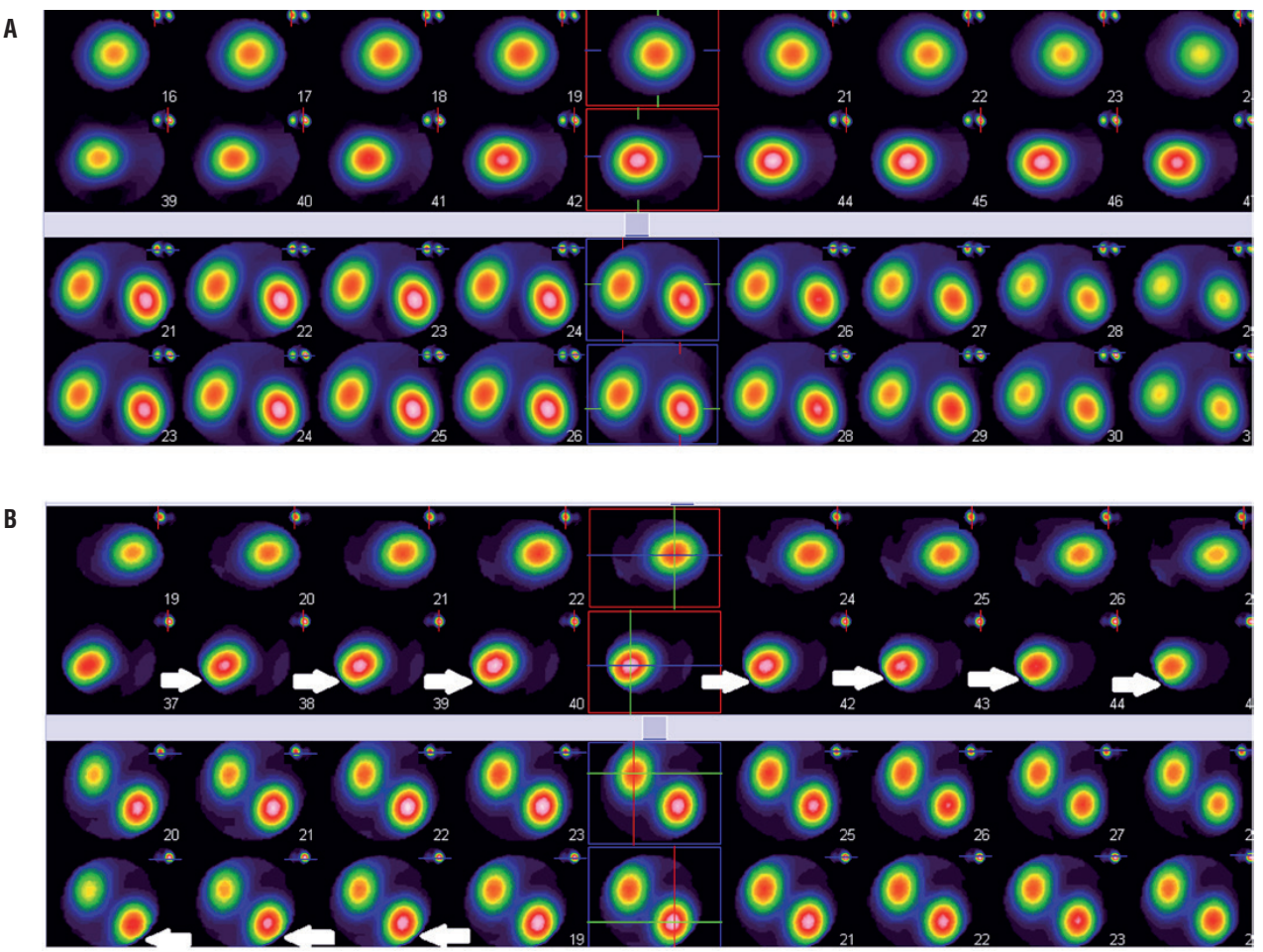


Figure 2 - (A) SPECT in the experimental group three months after delivery showed satisfactory results without any significant impairment as compared with control group; (B) SPECT in the control group showed that the renal injury persisted after three months of damage induction. The arrows demonstrate the damage in several sections while such impairment was not detected in experimental group.



It has been shown that the frequency of FMCT can be affected by histocompatibility between the mother and fetus (13). Approximately, 4 weeks post-gestation, FSCs can be detected in maternal circulation (14). In one study, the persistence of fetal leukocytes containing a Y body has been documented in the peripheral blood of women that were pregnant for the first time for more than 1 year after delivery (15). In another study in 1974, the persistence of fetal leukocytes in the maternal circulation was shown after gestation (16). In the study of Ciaranfi et al., noticeable male lymphocytes were detected in maternal blood of more than half of the women two years after delivery (17). In one study, it has been demonstrated that although the frequency of FSCs was higher in murine lungs during pregnancy, the number of fetal cells decreased significantly 21 days after delivery (18). In a recent study, GFP-positive cells were detected in 20% of the maternal spinal cord in first pregnancy; while it reached to 80% after the third pregnancy percent (19). Pregnancy-associated progenitor cells which have properties similar to stem cells and are found in injured and/or diseased tissues, persist in maternal blood and organs for decades after delivery

(3). Accordingly, the frequency of these progenitor cells reaches to its maximum level at 18-19th day of gestation (3).

FSCs have the capability to increase locally in the injured organ during and after pregnancy. In several maternal damaged tissues such as kidney, specific FMCT have been detected in both mice and humans. In the study of Khosrotehrani et al. the liver of a pregnant murine model was injured by carbon tetrachloride and it was demonstrated that the number of FSCs increased in the affected organ (20). In one study on GFP mice, Streptozotocin (STZ) was injected in order to induce maternal beta cell injury and investigate the persistence of FSCs in the pancreas. The results showed fetal DNA and $EGFP^+$ cells in maternal bone marrow, kidney, pancreas and liver (21). Recently, it was concluded that cigarette smoke exposure in the pregnant mouse model, leads to FSC retention in the maternal injured lung (22). In another study, functional blood vessels has been formed in maternal inflammatory skin by fetal endothelial progenitor cells during pregnancy (23). In the study of Wang et al., it has been shown that fetal GFP-positive cells migrate to damaged liver and kidney that were exposed to alcohol and gentamicin, respectively (24).

It has been demonstrated that the morphological appearances of the FSCs within different maternal tissues was similar to differentiated maternal cells in mice during pregnancy (18).

Their results were in accordance with the outcomes of the current study in which we revealed that the morphological appearance of FSCs in the damaged kidney after three months of delivery was indistinguishable from the maternal counterparts. In spite of the fact that no specific tissue marker was applied in the present study which is considered as one of the its limitations, the improvement of renal function, and the successful cell culture with the renal cell protocol can approve the differentiation of these FSCs to renal cells.

In the study of Perin et al. stem cells from human amniotic fluids were injected into embryonic kidneys of murine. The results demonstrated the potential of these stem cells to differentiate into renal vessels culminating in early development of the kidney (25). In spite of the fact that it has been mentioned that FSCs have an ineffective role on maternal health , the results of the current study expressed opposite results as confirmed by DMSA scan and SPECT. It has been shown that no significant improvement was detected in renal function of control group in which unpregnant rats were evaluated. The role of FSCs in functional improvement was not evaluated in previous articles which is one of the benefits of the current study. SPECT study may be also helpful when the size of the renal damage in small which cannot be detected with planer study. In the present study, this method was applied for the first time to estimate the renal function of rats in the field of FMCT.

In the present study, we sought to determine the prolonged persistence of FSCs in damage part of maternal kidney even after the pregnancy. Therefore, we decided to apply GFP-positive transgenic male rats to identify the FSCs more easily by their green color. Using this method, we achieved high sensitivity detection of FSCs in the section of the injured kidney. The ability of FSCs in migrating to damaged maternal tubular epithelial cells was demonstrated by immune histochemical analysis with anti-GFP antibody. The domiciliation of GFP-positive FSCs was confirmed by immunofluorescent microscopy according to their special immunofluorescent staining.

By PCR amplification of Y-chromosome sequences, we confirmed the persistence of FSCs in the blood circulation of the pregnant rat and the migration of Y-chromosome DNA of the male fetus to the damaged region of the kidney for further regeneration. In the present study, we confirm that FMCT may contribute to organ regeneration and repair. FSCs were only detected in injured region of the kidney and no FSC was distinguished in non-injured organs. These outcomes are in accordance with previous studies in which FSCs migrated to the maternal organs after induction of injury (20, 24). However, functional evaluation of the damaged organ was also studied to determine the role of FSCs in improvement of the impaired organ which was not previously evaluated in previous studies.

We developed a surgical model of renal injury during pregnancy in order to essay the fetal cell response in maternal damaged kidney. As the number of FSCs rise with the gestational age,

we decided to perform the renal damage at GD 11 which is in the middle of gestational period. In the current study, we showed that FSCs improved renal function and increased the proliferative response in the damaged kidney compared to the normal one.

This study has also other limitations. Although the trend of improvement in functional parameters can ensure a persistent outcome in tissue repair, renal specific markers were not applied. However, renal function improvement, and detection of Y chromosome and GFP-positive cells in the sub-cultured medium indicated the ability of FSCs in migration from the peripheral circulation to injured maternal kidney and differentiate into renal cells. Considering the fact that serum creatinine and glomerular filtration rate are easier and cheaper modalities in bilateral renal injuries, their application was not feasible in this model in which unilateral renal damage was created. So, we focused on imaging techniques rather than these laboratory tests.

While medical research teams are now trying to estimate the advantages and disadvantages of FMCT in human societies, this study demonstrated a perfect result of this phenomenon in functional improvement of the maternal damaged kidney in rat model. Therefore, we concluded that fetal GFP-positive cells have the potential to persist after delivery and domiciliate in injured kidneys with dynamic respond. It can be also realized that FSCs in maternal tissues have the ability to act as a reservoir of stem cells and pregnancy is a protection against susceptibility to several diseases. However, further studies are required to estimate the role of FSCs in repairing the maternal damaged organs by introduction of FSCs to maternal organ after harvesting and expanding the cells in vitro. Additionally, further investigations are required to estimate the efficiency of FMCT in human pregnancies.

CONCLUSIONS

In this study, we investigated the role of FSC migration and homing in their final destination in different target organs and tissue regeneration. We sought to characterize FSCs with multilineage potential that migrate to the maternal organs. The results of the current study revealed that FSCs play a crucial role in repairing maternal damaged kidney and improve its impaired function without prior in vitro manipulation. However, more studies are required to conclusively demonstrate the role of FMCT in human maternal damaged organs.

ABBREVIATIONS

FSCs = Fetal Stem Cells
GFP = Green Fluorescent Protein
DMSA = Technetium 99m-Dimercaptosuccinic Acid
SPECT = Single-photon emission computed tomography
FMCT = Fetal maternal cell trafficking

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CONFLICT OF INTEREST

None declared.

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The protective effect of Papaverine and Alprostadil in rat testes after ischemia and reperfusion injury

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ABSTRACT

Objective: To investigate the effect of papaverine and alprostadil on testicular torsion-detorsion injury in rats.

Materials and Methods: A total of 40 male Wistar-Albino rats were used in this study. Four hours of right testicular torsion was applied to each group, excluding sham operated group. The torsion-detorsion (T/D), T/D + papaverine and T/D + alprostadil groups received saline, papaverine and alprostadil at the same time as surgical detorsion, respectively. At 14 days after the surgical detorsion, ischaemic changes and the degree of damage were evaluated with Cosentino scoring and the Johnson tubular biopsy score (JTBS).

Results: JTBS was determined as 8.8±2.7 in the Sham group, 5.08±1.9 in the T/D+papaverine group, 5.29±2.3 in the T/D +alprostadil group and 2.86±1.9 in the TD group. The JTBS was determined to be statistically significantly high in both the T/D + papaverine group and the T/D + alprostadil group compared to the T/D group (p=0.01, p=0.009). In the T/D + papaverine group, 3 (43 %) testes were classified as Cosentino 2, 3 (43%) as Cosentino 3 and 1 (14 %) as Cosentino 4. In the T/D +alprostadil group, 5 (50 %) testes were classified as Cosentino 2, 3 (30 %) as Cosentino 3 and 2 (20%) as Cosentino 4.

Conclusion: The present study indicated that spermatic cord administration of alprostadil and papaverine showed a protective effect against ischemia/reperfusion injury after right-side testes torsion and histological changes were decreased after testicular ischemia reperfusion injury.

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INTRODUCTION

Testicular torsion is an urological emergency that may result in ischemia and necrosis of the testes. If not recognized in time, torsion may lead to ischemic injury and loss of the testes (1-3). Testicular damage varies depending on the grade and duration of the torsion (4).

To ensure blood flow, surgical detorsion is required in all cases. Reperfusion of the ipsilateral testes after ischemia results in overproduction of free oxygen radicals (FORs), cytokines, and adhesion molecules, in addition to the migration of leukocytes (5, 6). The main patho-

physiology of testicular torsion/detorsion (T/D) seems to be ischemia/reperfusion (I/R) injury of the testes. FORs and cytokines are major initiating components of the testicular injury. The administration of vasodilator drugs has potential antioxidant and therapeutic effects on I/R injury of the testes (7). To the best of our knowledge, no study has investigated the role of alprostadil in testicular I/R injury and only one study could be found in literature related to the protective effect of papaverine on testicular I/R injury. The aim of this study was to investigate the protective role of papaverine and alprostadil in testicular I/R injury.

MATERIALS AND METHODS

Following approval from the Local Ethics Committee (No: 4/5/15-367) a total of 40 male Wistar-Albino rats, each weighing 250-300 grams, were included in the study. All rats were fed with standard laboratory rat chow and water ad libitum on a 12 hour light/dark cycle at 21-24°C. All animals were handled in compliance with the recommendations of the animal care committee of the university and the Principles of Laboratory Animal Care (NIH publication No: 85-23, revised 1985).

Rats were randomly divided into 4 groups as follows: sham operated, torsion/detorsion group (T/D), T/D+papaverine group, and T/D+alprostadil group. The rats were anesthetized with the administration of 50mg/kg ketamine hydrochloride and 10mg/kg xylazine hydrochloride under aseptic conditions.

In the sham group (n=10), the right testes was removed through the incision and then replaced in the scrotum. In this group, no T/D procedure was performed. In the T/D group (n=10), saline (2mL of 0.9% NaCl) was injected by using 30 gauge needle into the spermatic cord at the same time as detorsion was applied. In the T/D+papaverine group (n=10), 2mL of papaverine (20mg/kg) was injected by using 30 gauge needle into the last 1cm part of the spermatic cord at the same time as detorsion. In the T/D+alprostadil (20µg/kg) group (n=10), 2mL of alprostadil was injected by using 30 gauge needle into the last 1cm of spermatic cord at the same time as detorsion. Torsion was induced by twisting the right-side testis 720 in a clockwise direction and this position was maintained for 4 hours by fixing the testes to the scrotum with 4/0 polyglactin (Vicryl; Ethicon Inc, Johnson&Johnson Co., Somerville, NJ,USA). At the end of the testicular ischemia period, the testes were released and restored to the normal position to allow reperfusion. After this operation, the rats were fed for 14 days and were then euthanised and right orchiectomy was performed. In the 14 day postoperative care period, 3 rats died in the T/D+papaverine group, so examination could only be made of 7 rats in that group.

The testicular tissue was fixed in 10% formaldehyde for histological analyses. Tissue sections of 4 micrometer thickness were stained with hematoxylin-eosin and evaluated by an experienced genitourinary pathologist. Ischaemic changes in the testes and the degree of damage were evaluated with Cosentino scoring (8) and the Johnson tubular biopsy score (JTBS). In Cosentino scoring, the testis is classified in 4 grades. Grade 1 to 4 stands for normal testis parenchyma to coagulation necrosis in the parenchyma. JTBS was developed to examine spermatogenesis histopatologically after testicular damaging circumstances. A Johnson score of 9 or 10 represents normal histology, a score of 8 hypospermatogenesis, 3-7 maturation arrest, 2 germinal cell aplasia and a score of 1, tubular fibrosis (9).

The data analysis was performed using SPSS for Windows, version 23.0 (SPSS Inc., Chicago, IL, USA). Conformity to normality of distribution was tested with P-P plot and Kolmogorov-Smirnov tests. Kruskal Wallis variance analysis was used for intergroup comparisons of continuous variables (Post hoc: Bonferroni), and the Chi square test was used for the comparison of categorical variables. Descriptive statistics for variables with non-normal distribution and nominal variables were presented as median (min-max) and the number of cases (n) and percentage (%), respectively. A value of $p<0.05$ was considered statistically significant.

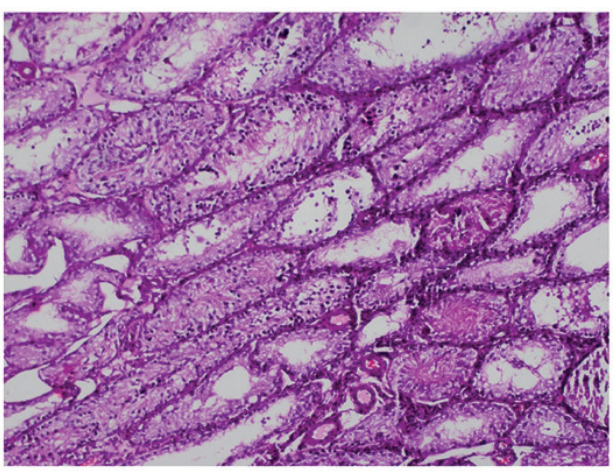
RESULTS

In the histopathological evaluation of removed right testes, 9 (90 %) testes in the sham group were determined as Cosentino Grade 1, and 1 as Grade 4. In the T/D group, 5 (50%) testes were

Cosentino Grade 3 and 5 (50%) were Grade 4. In the T/D+papaverine group, 3 (43%) testes were Cosentino Grade 2 (Figure-1), 3 (43%) were Grade 3 and 1 (14%) was Grade 4.

In the T/D+alprostadil group, 5 (50%) testes were Cosentino Grade 2, 3 (30%) were Grade 3 (Figure-2) and 4 (20%) were Grade 4 (Figure-3).

Figure 1 - Histopathology image of the testis parenchyma obtained from the papaverine group (Group 3) (Cosentino Grade 2).



The Cosentino scores of the T/D+papaverine group were determined to be better than those of the T/D group but the difference was not statistically significant (p=0.55). The Cosentino histopathological findings of the T/D+alprostadil group were observed to be significantly better than those of the T/D group (p=0.03). The Cosentino grades of the papaverine and alprostadil groups were seen to be similar (p=0.85).

The JTBS was determined as 5.08±1.9 in the T/D+papaverine group, 5.29±2.3 in the T/D+alprostadil group and 2.86±1.9 in the T/D group. The JTBS was determined to be statistically significantly high in both the T/D+papaverine group and the T/D+alprostadil group compared to the T/D group (p=0.01, p=0.009) (Figure-4).

DISCUSSION

Testicular torsion is a medical emergency seen in males, particularly in adolescence, but also

Figure 2 - Histopathology image of the testis parenchyma obtained from the alprostadil group (Group 5) (Cosentino Grade 3).

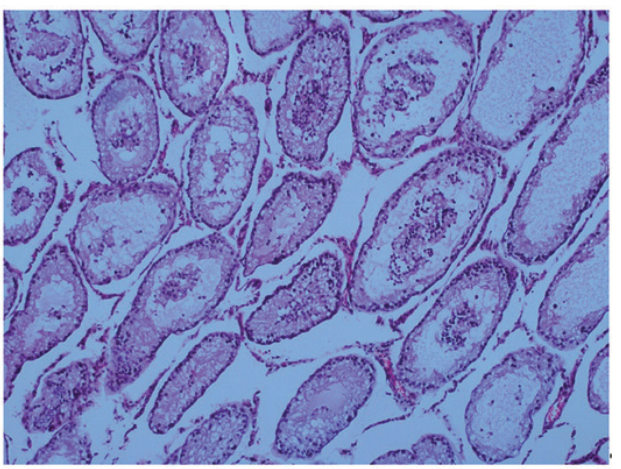
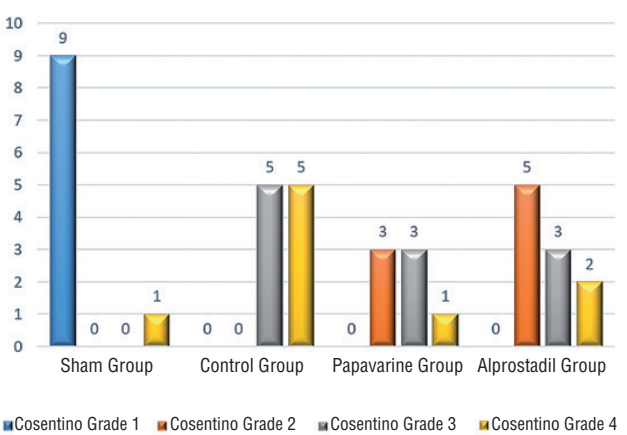


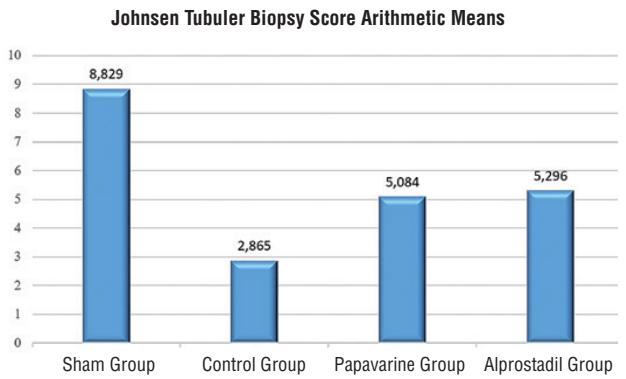
Figure 3 - Distribution of the groups according to Cosentino grades.



in childhood and young adulthood (10). To prevent loss of testicular function, surgical detorsion must be applied as an emergency in the treatment. It is necessary to obtain regular testicular blood flow to be able to continue normal spermatogenesis. Hypoxia is the main reason for testicular damage following testicular torsion (11). Although detorsion (reperfusion) provides correction of the blood flow, it can lead to additional dangers for the testis and this is known as reperfusion injury (12-15).

Reperfusion injury results in the formation of toxic FORs together with increased blood

Figure 4 - Distribution of the arithmetic means of the Johnsen Tubuler Biopsy Scores of the groups.



flow after ischaemia (12, 16). At the same time, a local and systemic inflammatory response develops. The complementary activation of leukocyte migration and platelet-leukocyte aggregation causes an increase in microvascular permeability (17-19). As a result of these events, testicular damage progresses further. To protect the testis from all forms of oxidative stress and I/R damage, many chemical agents have been tested in experimental studies. Despite successful results, it has still not been possible for these agents to come into clinical use as their use has not been possible on humans because of severe side-effects (7, 20).

Papaverine is an opium alkaloid used in the treatment of vasospasm and erectile dysfunction (15). Papaverine has also been used by direct application to the blood vessels as a smooth muscle relaxant in microsurgery. By inhibiting phosphodiesterase enzyme, the adenosine monophosphate (cAMP) level is usually increased. Another important effect which is formed is a change in mitochondrial respiration (14, 21). Some researchers have stated that sildenafil and other phosphodiesterase inhibitors may have anti-inflammatory properties by inhibiting ROS, leukocyte infiltration and inflammatory cytokines such as IL-1, IL-6 and TNF (22, 23).

The effect of alprostadil, which is a PGE1 analog, is shown through an increase in adenosine monophosphate (cAMP) with adenylate cyclase activation and by lowering the intracellular Ca^{++} level. With this effect, alprostadil leads to relaxation in the smooth muscle wall. Alprostadil provides an immunosuppressive and cytoprotective effect with a reduction in leukocyte aggregation and a decrease in TNF expression. Increasing levels of TNF, P-selectin, E-selectin, ICAM-1 and VCAM-1 in ischaemia and reperfusion are significantly reduced with a PGE1 infusion (24). Therefore, activation and degranulation of macrophages and granulositis decrease. In transplanted pulmonary tissue, PGE1 has been shown to reduce the hypothermic thermal effect of ischaemia reperfusion damage and provide protection by increasing the acquisition of glucose and oxygen (25). This effect of PGE1 applied during reperfusion has been shown to be achieved by reducing pro and anti-inflammatory cytokine levels.

In previous studies that have evaluated ischaemia-reperfusion injury in different organs with papaverine and alprostadil, the drugs have been administered intravenously, intra-arterially or intraperitoneally. In the current study, considering that the dilatation effect could be greater in vascular structures, it was thought appropriate to administer papaverine and alprostadil directly into the spermatic cord.

For the histopathological evaluation of testicular deterioration in this study, Cosentino scoring and JTBS were used. In Cosentino scoring, the testis is classified in 4 grades. While Grade 1 shows normal testis parenchyma, Grade 4 testis shows coagulation necrosis in the parenchyma. Johnson et al. developed the JTBS to be able to evaluate spermatogenesis quantitatively following any event which has caused damage to the testis, and this is the currently most widely used scoring system in routine applications. This score gives a score for each seminiferous tubule in the biopsy material and the mean value is calculated for the examined tubules. A Johnson score of 9 or 10 represents normal histology, a score of 8 hypospermatogenesis, 3-7 maturation arrest, 2 germinal cell aplasia and a score of 1, tubular fibrosis (9).

In the revision of literature, it was found that protective effects of alprostadil were not evaluated before, by injection directly into spermatic cord, in a testicular T/D model. In the sham group, 9 testes were evaluated as Cosentino Grade 1 and 1 as Grade 4. The coagulation

necrosis seen in 1 was probably related to artery damage during surgery. In 50% of the rats applied with alprostadil, there was a mild degree of deterioration in the alignment of germ cells in the seminiferous tubules and a loss of cohesion in the cells (Grade 2). Only 2 of the testes were Cosentino Grade 4. A significant degree of improvement was observed in the mean JTBS in the alprostadil group compared with the control group (p=0.009).

In the revision of literature, it was found that only one study which has attempted to determine whether or not papaverine has a protective effect on I/R injury in the testes; 35 rats were separated into 5 groups (control, sham-operated, verapamil-treated, lidocaine-treated and papaverine treated). In that study, papaverine did not show any protective effect in respect of sperm count, motility or morphology (26). In contrast, in the current study, the JTBS of the papaverine group was determined to be significantly higher than that of the T/D group. Cosentino Grade 2 was determined in 3 (43%) rats of this group. Although a histopathological improvement was seen compared to the T/D group, the difference was not statistically significant. However, as the evaluation of this group was made on 7 rats, there could be Type II error in the findings.

CONCLUSIONS

In the results of the current study, a significant improvement was observed in the JTBS with the application of both papaverine and alprostadil. Protective effects were determined histopathologically in the Cosentino grades with both drugs, although papaverine was not statistically significant. According to these results, these drugs applied to the spermatic cord during detorsion in rats have a useful, protective effect on testicular injury. To clarify the protective effects of these drugs, there is a need for further studies using different doses and different administration pathways.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: The protective effect of Papaverine and Alprostadil in rat testes after ischemia and reperfusion injury

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In testicular torsion (TT), not only the ischemia due to TT but also the reperfusion during detorsion, both phenomena lead to testicular damages, so-called ischemia/reperfusion (I/R) injuries. Many drugs can help to protect these injuries, specially the antioxidants.

The authors in this article (1), using Cosentino score (CS) and Johnson tubular biopsy score (JTBS) to analyze the I/R testicular injuries, in rats submitted to TT maintained for four hours and applying papaverine or alprostadil directly to the spermatic cord during the surgical detorsion, demonstrated the protective effects of both drugs on the I/R injuries. JTBS demonstrated that both drugs had significant protective effects, but CS demonstrated that only alprostadil showed statistically significant protective effects. So, alprostadil seems to be better than papaverine for this purpose.

In the clinical practice, there is a need for more studies in order to accept, as a guideline, the use of the alprostadil or papaverine as having protective effects on testicular I/R injuries.

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SURGICAL TECHNIQUE

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Ureteroileal bypass: a new technic to treat ureteroenteric strictures in urinary diversion

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ABSTRACT

Objective: To present our technique of ureteroileal bypass to treat uretero-enteric strictures in urinary diversion.
Materials and Methods: One hundred and forty-one medical records were reviewed from patients submitted to radical cystectomy to treat muscle-invasive bladder cancer between 2013 and 2015. Twelve (8.5%) patients developed uretero-enteric anastomotic stricture during follow-up. Five patients were treated with endoscopic dilatation and double J placement. Four were treated surgically with standard terminal-lateral implantation. Three patients with uretero-enteric anastomotic stricture were treated at our institution by "ureteroileal bypass", one of them was treated with robotic surgery.
Results: All patients had the diagnosis of uretero-enteric anastomotic stricture via computerized tomography and DTPA renal scan. Time between cystectomy and diagnosis of uretero-enteric anastomotic stricture varied from five months to three years. Mean operative time was 120±17.9 minutes (98 to 142 min) and hospital stay was 3.3±0.62 days (3 to 4 days). Mean follow-up was 24±39.5 months (6 to 72 months). During follow-up, all patients were asymptomatic and presented improvement in ureterohydronephrosis. Serum creatinine of all patients had been stable.
Conclusions: Latero-lateral ureter re-implantation is feasible by open or even robotic surgery with positive results, reasonable operation time, and without complications.

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INTRODUCTION

Bladder cancer is the ninth most frequently diagnosed cancer worldwide, with the highest incidence rates observed in men in Southern and Western Europe and North America (1). Approximately one third of patients diagnosed with bladder cancer have muscle invasive disease (MIBC). The standard definitive treatment for MIBC is radical cystectomy (RC) with pelvic node dissection and urinary reconstruction (2, 3).

Complications of RC and diversion can appear after months or years of surgical treatment. Most complications can be managed conservatively, but some of the late adverse events require surgical treatment. Uretero-enteric strictures are a late complication after cystectomy and diversion that occur in 2% to 15% of patients (4-6). Multiple treatment alternatives have been proposed to those strictures with variable success rates. Ureteral reimplantation is still considered the gold standard surgical treatment (7). However, the surgical approach to the uretero-enteric anastomosis can

be challenging due to fibrosis and adhesions. We propose herein a technical modification aiming to minimize ureteral dissection; the technique involves a latero-lateral anastomosis of the dilated ureter with the ileal conduit without detaching the ureter from the intestinal segment. Our experience with this technical modification is described.

MATERIALS AND METHODS

Twelve (8.5%) patients developed ureteroenteric anastomotic stricture among 141 patients submitted to radical cystectomy to treat MIBC between 2013 and 2015 in our institution. Bricker's procedure is used in external ileal conduit diversion, and, Studer's technique, in ileal neobladder. In both diversions, the ureter is reimplanted separated with 2 continuous running sutures.

Follow-up after radical cystectomy was (mean: 13.2 months, 3-38 months). Patients were evaluated 3 months after surgery, and 6 months successively, with CT scan and serum creatinine; if there was any progressive hydronephrosis, an increase in serum creatinine, lumbar pain, or pyelonephritis, a DTPA renal scan was evaluated.

None of these patients were treated with radiotherapy

In all of them a percutaneous procedure was attempted as treatment, but was possible in only five patients, since they weren't completely stenotic. Seven patients were treated surgically; four of them were treated with a resection of the stenotic area and a standard terminal-lateral implantation. The last three patients in this series were treated by a "latero-lateral anastomosis" and were the objective of this publication. Before surgery, the technique was explained to patients, and informed consent was applied. There was no selection of patients for this technique.

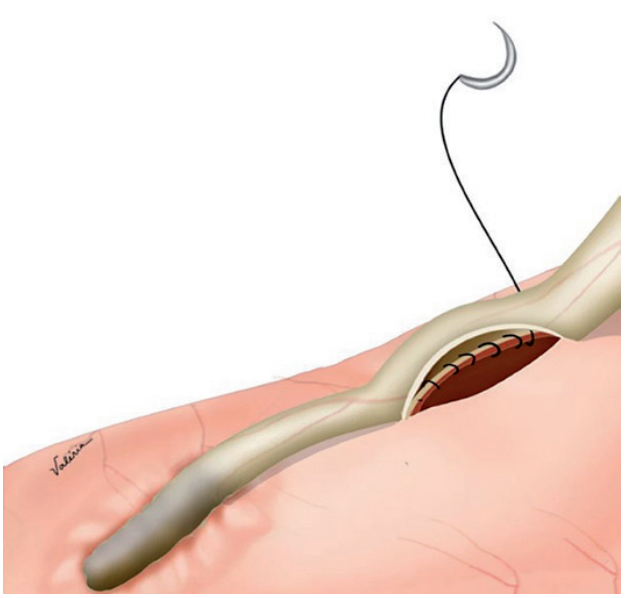
Technique of latero-lateral ureter re-implantation

The surgery begins with the lysis of adhesions, and the identification of diversion. The stenotic area at the anastomosis site is identified without any prior catheter placement, and left in place without excision. The proximal portion of the dilated ureter is dissected, and mobilized; (Figure-1).

Figure 1 - Ureter mobilization.

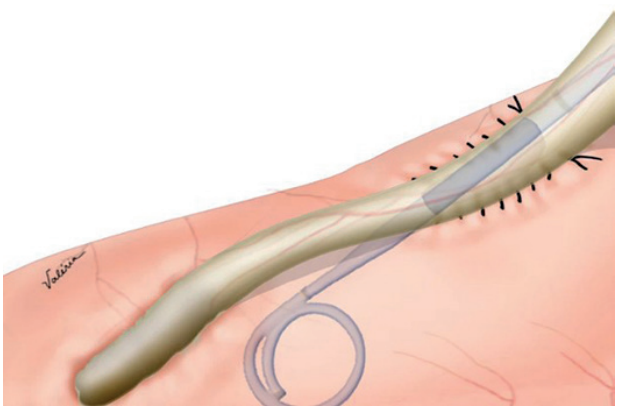
A 1cm incision is performed in the lateral wall of the ureter and at the urinary diversion; a latero-lateral anastomosis is performed with 2 continuous 5-0 polyglactin sutures (Figure-2). The posterior side of anastomosis is made first, then a

Figure 2 - Anastomosis in urinary diversion.



double J catheter 6x26 is placed (Figure-3), and finally the anterior side is sutured. A peritoneal drain is placed. The double J catheter is removed after 4 weeks of the surgery.

Figure 3 - ureter-ileal bypass with 2J catheter.



RESULTS

Two patients had ileal conduits and one had an orthotopic ileal neobladder done by Studer's technique as an urinary reconstruction after cystectomy. Two patients were symptomatic (flank pain and pyelonephritis) and one was asymptomatic. All patients had the diagnosis of uretero-enteric anastomotic stricture with grade 3 hydronephrosys (8) on the computed tomography scan (CT), without any image of cancer recurrence, and obstructive curves on DTPA renal scan. One renal unit was affected in each patient: two at the right and one at the left side.

Time between cystectomy and the diagnosis of stenosis was five months to three years (3 years in the first case, 18 months in the second and 5 months in the third case).

Mean operative time was 120±17.9 minutes (98 to 142 min) and hospital stay was 3.3±0.62 days (3 to 4 days). There weren't any post-operative complications (Clavien-Dindo Classification (9)) in these patients. Mean follow-up was 29.3 months (10 to 48 months).

During follow-up, patients were evaluated 3 months after surgery, and 6 months successively, with CT scan and serum creatinine. All of them were asymptomatic and had improvement in the ureterohydronephrosis. Two cases still had minor ureterohydronephrosis, and were submitted to DTPA, which proved that there was no obstruction. One patient had completely resolved ureterohydronephrosis and no further exams were necessary. During follow-up, all patients were asymptomatic. Serum creatinine of all patients was stable (Table-1).

Comments

The uretero-enteric anastomotic stricture occurs commonly within the first 1-2 years postoperatively, regardless of the type of implant (10, 11). The incidence is cumulative over time, and stenosis has been reported up to 6 years postoperatively (12).

Patients can be asymptomatic, present with an insidious onset, or be detected by an increased serum creatinine or from regular follow-up imaging exams. Some patients present flank pain. Pyelonephritis is usually a late manifestation that accom-

Table 1 - Study Group Carachteristics.

AA	Cr (mg/dL) pre-cistectomy	Urinary Diversion	Cr (mg/dL) post-cistectomy	Symptoms	Side	Cr (mg/dL) post-re-implatation	Follow-up (months)
67 years	0.69	OIN	1.0	Flank pain	R	0.9	48
75 years	0.60	IC	1.6	Pyelonephritis	R	1.1	30
70 years	0.88	IC	1.34	None	L	1.2	9

AA = age at analysis; **OIN =** orthotropic ileal neobladder; **IC =** Ileal Conduit; **R =** Right; **L =** Left

panies long-standing obstruction with grade 4 nephropathy and renal parenchymal loss (13-18).

Even with the upper tract dilation, the diagnosis may be challenging. Frequently a dynamic imaging exam is needed, such as a CT urography, DTPA renal scan, anterograde nephrostogram, or loopogram/neobladder cystography. Most commonly the left ureteral implantation is affected, due to a wider mobilization of the ureter (17, 18).

The upper tract dilation may be a result of recurrent malignancy. Certainly, all cases of obstruction must be rigorously investigated to rule out ureteral luminal recurrence or retroperitoneal metastatic spread of the disease. This can be done using CT and magnetic resonance image, and in suspicious cases of cancer recurrence, cytology or even biopsy are necessary (18, 19).

But the most common cause is a stenotic process at the ureteric reimplantation site due to an ischemic condition as a consequence of ureteric dissection or after radiation (18-21).

Recently, due to advances in invasive radiology and endourology percutaneous imaging guided procedures, endoscopic techniques have been an option in treatment (22). The referred success rate widely varied; balloon dilation (16%-83%), (23-30); endoureterotomy (30%-50%), (26) and/or stent placement (45%) (31).

Laparoscopic or even open surgery after cystectomy can be challenging due to the presence of intra-abdominal adhesions and modified anatomy after reconstruction (4). However, the standard management is an open surgical revision with excision of the strictures ureteral segment and wide reanastomosis. The reported success rates are between 76% and 93% in 3 years, with acceptable morbidity (5, 19).

Benign ureteral strictures are a result of an ischemic insult and the key to their prevention and management is meticulous surgical technique. During its repair, pouch mobilization and identification of the stenotic area may be a difficult procedure.

The rationale of a latero-lateral anastomosis is to perform a minimal ureteric dissection and mobilization to avoid compromising even more its blood supply (32). The stricture is not excised and a proximal latero-lateral anastomosis is easily created between the dilated ureter and the bowel segment. The procedure may be performed by an open approach or by a minimally laparoscopic/robotic approach as described in our series.

This is an initial series with few cases, which precludes the statistical comparison of results with any other series, such as with a series of cases in which they were reimplanted with the standard technique. The safety of the new technique shown in the initial cases allows its use in the following cases, and soon we will have a series for comparison.

CONCLUSIONS

Latero-lateral uretero-enteric anastomosis is a feasible treatment option for benign anastomotic strictures with encouraging midterm outcomes. It can be performed either by open or by minimally invasive approaches with good perioperative outcomes.

CONFLICT OF INTEREST

None declared.

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Laparoscopic approach to pheochromocytoma in pregnancy: case report

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ABSTRACT

A 32-year-old 22-week pregnant hypertensive woman with sporadic episodes of headaches, sweating, and facial flushing was diagnosed with pheochromocytoma through biochemical and imaging tests. Perioperative management included a multidisciplinary approach, symptom stabilization with α blockade followed by ß blockade, and tumor resection by laparoscopic adrenalectomy at 24 weeks gestation. The diagnosis was confirmed by histopathological examination and immunohistochemistry tests. The decision for surgical removal of the tumor was based on maternal symptoms, tumor size, gestational age, the possibility of doing a laparoscopy, and the expertise of the surgical team.

ARTICLE INFO

Keywords:
Pheochromocytoma; Pregnancy; Laparoscopy

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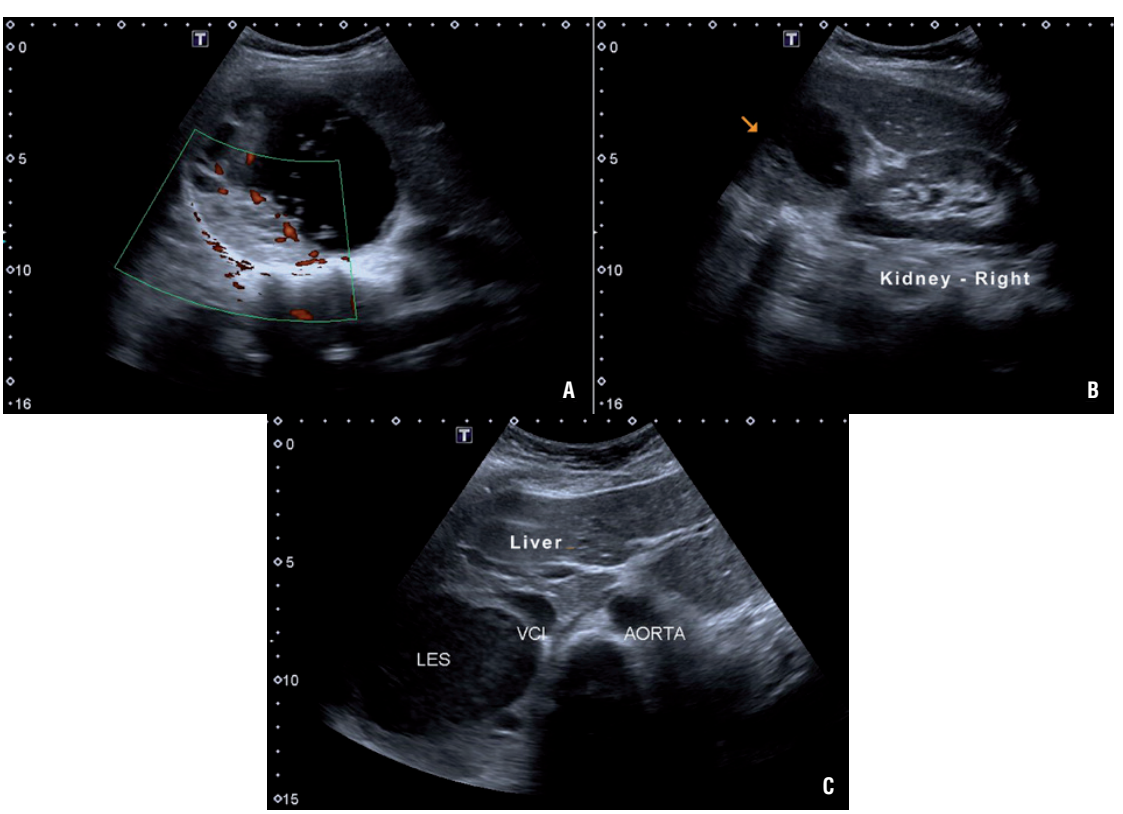
INTRODUCTION

Pheochromocytoma (PCC) is a neuroendocrine tumor derived from chromaffin cells and located within the adrenal medulla in approximately 90% of cases (1). Although extraordinarily rare during pregnancy with a reported incidence less than 0.2 per 10,000 pregnancies, PCC should be considered when severe hypertension occurs before 20 weeks gestation or when hypertension is associated with disease symptoms such as headaches, palpitations, and diaphoresis (2). PCC in gestation, when untreated, raises maternal and fetal mortality to up to 50% (3, 4). However, early diagnosis and appropriate treatment reduce maternal mortality to less than 5% and fetal mortality to below 15% (3, 5). The diagnosis can be established by detecting elevated levels of catecholamines and their metabolites in plasma or urine. Ultrasound and magnetic resonance imaging (MRI) are the preferred imaging modalities for tumor localization during pregnancy (6). Surgery is the definitive treatment for PCC after management of hypertension with **α** blockade, but the timing of tumor removal depends on the gestational age, the severity of maternal symptoms, and the risks associated with pregnancy termination (4).

CASE PRESENTATION

A 32-year-old Caucasian woman at 22 weeks of gestation with singleton live fetus presented 5 weeks prior with sporadic episodes of headaches, facial flushing, and sweating. The obstetric ultrasound showed a healthy fetus. Her first pregnancy four years earlier was complicated by severe preeclampsia at 34 weeks gestation for which she was induced and delivered by emergency cesarean section. Since then, she was treated with methyldopa 500 mg/day, but her blood pressure was not monitored and she had no other complaints or complications. She was not on any regular medications, was not a smoker or an alcohol user, and there was no history of illicit drug use nor family history of multiple endocrine neoplasia (MEN). Due to palpitations, nine months earlier she underwent a cardiac stress test, which detected sustained supraventricular paroxysmal tachycardia, followed by an electrophysiology study that failed to reveal any disorder or dysfunction. The echocardiogram was also normal. Symptoms of headaches, facial flushing, and sweating started at 17 weeks gestation. Routine laboratory tests revealed a fasting glucose of 92 mg/dL and serum creatinine of 0.5 mg/dL. Complete blood count, sodium, potassium, calcium, phosphorus, AST, ALT, total cholesterol and fractions, TSH, free T4, urinary sediment levels, serum aldosterone, calcitonin, parathyroid hormone (PTH), and cortisol were all normal. However, metanephrine and normetanephrine on 24 hours urine collection were 6873.2 µg/24 h (reference value <280 µg/24 hours) and 6299.2 µg/24 hours (reference value <732 µg/24 hours), respectively. Ultrasonography of the abdomen revealed a 10.1 × 9.5 cm mass in the right adrenal gland consistent with PCC (Figure-1). Blood pressure was con-

Figure 1 - A) Ultrasound showing right adrenal tumor with more than 10 centimeters, with mixed cystic-solid components and doppler imaging confirm the presence of vascular flow; B) Arrow indicating the great mass between the liver (Liver) and the right kidney (Kidney - right**); C) Pheochromocytoma (LES) by compressing and pushing the inferior vena cava (VCI).**



trolled with prazosin 2 mg/day for 10 days followed by propranolol 20 mg/day for four days, when a consultation by a multidisciplinary team, including surgeons, anesthesiologist, obstetrician, and endocrinologist, was held to determine the most appropriate management. The surgical approach selected was laparoscopic transperitoneal right adrenalectomy due to the considerable experience of the surgical team with the technique, the patient's significant symptoms, and the gestational age (second trimester, 24 weeks gestation at the time of surgery). The patient was placed in a modified flank position, 45 degrees back from vertical. Three ports were used in triangulation, and an additional fourth port for the liver retraction. The patient received combined epidural and general anesthesia with an epidural catheter placed for postoperative analgesia and was continuously monitored with a cardioscope, pulse oximetry, invasive arterial pressure monitoring from the radial artery, and capnography. Serial arterial blood gases and glucose were monitored to prevent maternal acidosis and hypoglycemia. Central venous access was accomplished via her right jugular vein for administration of liquids and vasoactive agents. General anesthesia was maintained with continuous remifentanil and propofol infusion. Special consideration was taken with pneumoperitoneum pressure, which was maintained below 12 mmHg for nearly the entire duration of surgery and was only raised to 15 mmHg for a few minutes during vessel dissection to prevent a reduction in uteroplacental blood flow. During dissection of the adrenal vessels, a sodium nitroprusside infusion (0.8 µg/kg/min for approximately 7 min.) and intermittent boluses of esmolol 10 mg IV (total 20 mg) were used to control mean arterial pressure (MAP reduced from 136 mmHg to 83 mmHg) and heart rate (lowered from 133 bpm to 86 bpm). An ultrasonic dissector - Harmonic scalpel™ (Ethicon Endo Surgery INC - Johnson & Johnson, NJ, USA) was used for adrenal gland dissection. Blood loss was less than 50 mL. The patient remained normotensive for the remainder of the surgery and postoperatively. The operative time was 120 min and no complications were recorded. The patient was extubated immediately after surgery with good pain control, and the epidural catheter was removed on the same day of surgery. Obstetric ultrasound performed soon after anesthesia recovery revealed no abnormalities. Antihypertensive therapy was not required postoperatively or during the remainder of pregnancy. The patient was discharged on postoperative day four with no symptoms and normal blood pressure.

Histopathological examination and immunohistochemistry tests (positive chromogranin A and synaptophysin staining) confirmed the diagnosis of PCC.

Five weeks after surgery, while remaining normotensive without antihypertensive drug therapy, the patient was admitted due to premature rupture of membranes, and one day later suffered placental abruption with severe bleeding. She underwent emergency cesarean section but the newborn, who was born alive, died prematurely within 48 hours.

DISCUSSION

PCC in pregnancy can cause fatal hypertensive crisis that can be triggered by vaginal delivery, general anesthesia, the physical effects of the enlarging uterus, uterine contractions, or fetal movements (2), and may impose a serious risk to the fetus because extreme vasoconstriction in the uteroplacental circulation may result in intrauterine hypoxia and premature placental abruption (5). Undiagnosed and/or untreated PCC carry a risk of mortality for both mother and fetus as high as 58% (4, 6).

Symptoms may occur for the first time in pregnancy due to increased vascularity of the tumor and/or mechanical factors such as pressure from the enlarging uterus or fetal movements, which can stimulate catecholamine secretion (7, 8). These signs and symptoms include hypertension (98% of cases), orthostatic hypotension, palpitations, headaches, sweating, anxiety attacks, facial flushing, and chest pain (5, 6). However, in pregnant women, the disease can be mistaken for other causes of hypertension, especially specific hypertensive disorders of pregnancy such as preeclampsia (3). In the current case, preeclampsia in the previous pregnancy may have been the first manifestation of PCC, but this hypothesis was not investigated at the time.

Detecting elevated levels of catecholamines and their metabolites in plasma and urine establishes the diagnosis of PCC. Once a diagnosis has been confirmed biochemically, ultrasonography and MRI are the preferred modalities of tumor localization for the safety of the fetus (2, 4, 5).

The success of treatment will depend on the appropriate preoperative medical management, which should always be started with α-adrenergic blockade (phenoxybenzamine or prazosin) for adequate control of blood pressure (9). Pre-surgical preparation with this class of drugs is one of the main reasons why surgical mortality has decreased over the last 30 years to <3% (5). Even though there is no consensus regarding the optimal duration of medical pretreatment, it should be given for 10–14 days or until a stable hemodynamic condition is achieved. In case of tachyarrhythmias, β-adrenergic blockade should only be started after some days of appropriate α-adrenergic blockade (2, 4, 7). A collaborative multidisciplinary team, including surgeons, anesthesiologist, obstetrician, and endocrinologist, is decisive for case management (10). Surgical resection of the tumor is the definitive treatment for PCC, which can be achieved either by open, laparoscopic, or robotic approaches (1, 6, 8). Laparoscopic adrenalectomy is the surgical approach of first choice if tumor size is <7 cm (4, 10, 11); this is a safe procedure with a complication rate <8% (5, 9). Although the posterior retroperitoneoscopic approach seems to be a good alternative for adrenalectomy than laparoscopic transperitoneal approach, avoiding the need to enter the peritoneal cavity, there is no evidence that supports the superiority of one over the other, both showing similar low morbidity and mortality (11). The choice of surgical approach must be based mainly on the expertise of the surgical team and the greater maternal and fetal safety. In this case, laparoscopic transperitoneal approach was chosen, considering the greater experience with this technique by the surgical team, as well as the unfeasible prone position of pregnant patient to perform a posterior retroperitoneoscopic approach.

Timing of tumor excision in pregnant women will depend on the gestational age at which diagnosis is made, fetal development, and the severity of maternal symptoms. Surgery should be avoided in the first trimester – as organogenesis is incomplete and miscarriage is highly likely – as well as in the third trimester – because by then the enlarging uterus precludes adequate access and visualization of the abdomen (12). Thus, the second trimester is recommended as the ideal time for surgical intervention. Surgical removal is recommended before 24 weeks of gestation (3, 5, 7, 8). However, after 24 weeks of gestation, the patient can be treated with the appropriate α-adrenergic blockade until the fetus is viable, when the tumor can be removed after an elective cesarean section (4, 7, 8). In the current case, following a multidisciplinary consultation and with the patient's consent, and having been treated with prazosin for 10 days, she underwent laparoscopic adrenalectomy at 24 weeks gestation.

Pregnancy was previously a contraindication to laparoscopy because of concerns regarding the potential effect of carbon dioxide on the developing fetus and the safe entry into the abdominal cavity due to the displacement of anatomy by the gravid uterus. Additionally, increased abdominal tension by the pneumoperitoneum could reduce the vena cava and the uteroplacental blood flows (1, 8). Nevertheless, previous concerns surrounding the potential adverse hemodynamic effects associated with pneumoperitoneum were unjustified, because these changes were no different when compared to open adrenalectomy (2). Moreover, catecholamine concentrations increase to a lesser extent with laparoscopic than with open adrenalectomy (2). Thus, laparoscopy is currently the safest adrenalectomy approach even for this high-risk population. Laparoscopy is a less invasive procedure that results in faster functional recovery, shorter hospital stay, and early ambulation, reducing the risk of thromboembolism and the need for opioid painkillers, which can affect fetal development. In addition, return of gastrointestinal function is also more rapid than with an open procedure (10, 11). Small incisions decrease the potential for herniation with the increased pressure of the gravid uterus and, in addition, laparoscopy offers enhanced visualization without manipulating the uterus, resulting in reduced risk of preterm labor (1, 2, 5, 8). These benefits combined with the expertise of the surgical team and a multidisciplinary approach make laparoscopy a safe, effective, and minimally invasive option for adrenalectomy for PCC in pregnancy (1).

Importantly, perioperative management includes treatment of both mother and fetus (4). In the current case, management was effective, without intra or postoperative complications, resulting in complete resolution of the disease. Despite the perinatal fetal demise, maternal safety was preserved and delaying surgical resection could have increased the risk of catastrophic complications in late pregnancy.

CONCLUSIONS

PCC is a rare but important cause of hypertension in pregnancy. It should be included and investigated as a differential diagnosis in cases of labile hypertension in pregnant women with or without associated symptoms, because inadequate treatment considerably increases maternal and fetal mortality. Management of PCC during pregnancy should be discussed on a case by case basis by a multidisciplinary team. Surgical resection is recommended during the second trimester of pregnancy. Considering its benefits and the expertise of the surgical team, laparoscopic surgery is the favored technique.

CONFLICT OF INTEREST

None declared.

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Salvage surgical procedure for artificial sphincter extrusion

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ABSTRACT

Case Hypothesis: Surgical removal is the standard treatment for artificial sphincter extrusion. However in some specific situations is possible to maintain the prosthesis with good results.
Case report: We report a 60 years old patient presenting sphincter pump extrusion one month after artificial urinary sphincter (AUS) AMS 800™ placement for treating post-radical prostatectomy urinary incontinence (PRPUI). He also had a penile prosthesis implant one year before that was replaced in the same surgery the sphincter was implanted. As patient refused sphincter removal and there were no signals of active infection he was treated by extensive surgical washing with antibiotics and antiseptics. Pump was repositioned in the opposite side of the scrotum. Patient had good evolution with sphincter activation 50 days later. After 10 months of follow up, patient is socially continent and having regular sexual intercourse. Savage surgery may be an option in select cases of artificial sphincter extrusion.
Promising future implications: Like in some patients with penile prosthesis some patients with artificial sphincter extrusion can be treated without removing the device. This may be a line of research about conservative treatment of artificial sphincter complications.

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SCENARIO

We described the case of a 60 years old male submitted to Radical Prostatectomy 8 years ago. All the surgical margins were negative and postoperative PSA remain lower than <0.003ng/dL. The patient also had diabetes type II and hypertension under good clinical control. Since the catheter removal patient presented severe urinary incontinence and severe erectile dysfunction. Pelvic floor rehabilitation was attempted without success. Patient had a continuous leakage during the day. During the night he improved continence and was able to void twice a night with a good urinary stream even though he needed to use one pad/night. Urodynamics showed a good bladder capacity with a Valsava leak point pressure of 35 centimeters of water. He was not able to elaborate a voiding diary once he leaked most part of the day.

After one year, he was treated by artificial sphincter placement with an improvement of 80% in continence (he reduced the number of pads/day from 6 to one or two). However, he remained wearing 1-2 pads a day and he was unsatisfied with his quality of life.

After 2 years, a second cuff placement was attempted and patient developed urethral fistulae requiring removal of all the artificial sphincter system. The fistulae were treated by a silicone Foley catheter placed in the urethra during 14 days.

Six months later, he underwent a new sphincter placement associated to semi rigid prosthesis implantation in order to treat the incontinence and the erectile dysfunction. He had new urethral extrusion requiring all artificial sphincter system removal but remained with the penile prosthesis.

Patient remained totally incontinent wearing up to 10 pads a day. Patient also referred no sexual activity due to incontinence.

Urodynamic evaluation showed severe sphincter deficiency (Valsalva leak point pressure = 45cmH_2O). Cystourethrogram showed no urethral stenosis.

He was then submitted to new sphincter placement using a transcorporeal cuff. Urethral integrity was confirmed by an urethrocistoscopy carried out just at the beginning of the procedure. The surgery was uneventful but during the surgery we had to implant the pump through a scrotum incision due to extensive local fibrosis caused by previous surgeries.

One month after this new intervention, patient developed pump extrusion through the scrotum. There was just a discrete local secretion and no signs of systemic infection (Figure-1).

As the patient refused the standard treatment (removal of all system) we took him to operating room and under general anesthesia we carried out an extensive wound clean with antibiotics solution (cephalosporin and gentamicin solutions) as well as with chlorexidine solution. In addition, we did a surgical removal of all inflammatory tissue around the pump tubes and moved the pump to the opposite side of scrotum (right side). Patient received large spectrum IV antibiotics (Ceftriaxone plus vancomicin) during 3 days. After that, he was discharged with oral ciprofloxacin during 14 days.

Patient had a good evolution, without signals of local or systemic infection attested by local examination, urinalyses, hemogram and PCR. The sphincter was activated after 8 weeks.

Currently, after 14 months of follow up, the local aspect is excellent (Figure-2) and blood and urine tests are normal. Patient is socially continent, wearing one pad a day and resumed his sexual life resulting in a great quality of life.

Figure 1 - Initial aspect showing the pump extrusion through the scrotum skin. Note the absence of inflammatory signs or secretion.

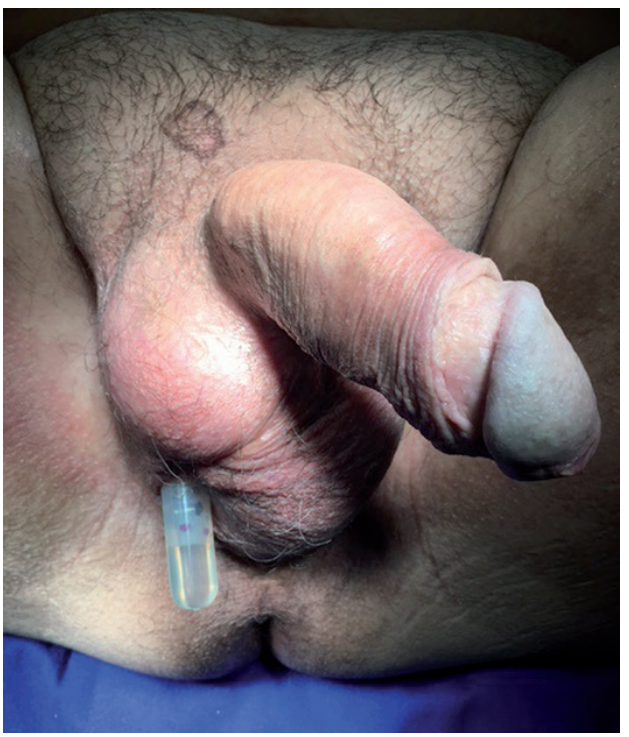

Figure 2 - Ten months of follow up after the last surgery. Note the pump under the skin in the left side and no signals of infection or erosion.

CASE(S) HYPOTHESIS AND RATIONAL

Urinary Incontinence is the most devastating long term complication of radical prostatectomy in terms of patients' quality of life (1).

The artificial urinary sphincter AUS is considered the gold standard treatment for this condition (2). The most representative series evaluating the artificial sphincter AMS 800 for the treatment of PRPUI shows this procedure is effective in almost 90% of the patients suffering from post prostatectomy urinary incontinence (3). The efficacy of this method can be summarized in Table-1 (4). However, complications may occur in about 15% of the patients treated with this procedure. These complications include mechanical failure in 5%, erosion in 5% and infection in another 5% (4). Table-2 summarizes these data in different publications (4). In cases of mechanical failure the broken part or the whole system can be removed and replaced in the same procedure. On the other hand, in cases of erosion and infection, the standard treatment is the sphincter removal and new sphincter implantation after three or more months. The rational for this approach is that removal of the synthetic components allows the antibiotics together with immunological system to eliminate all the bacteria and allowing a safe new implantation. However, patients submitted to sphincter removal due to erosion have a higher complications rate and a higher chance of new erosion (5).

Penile implant represents another example of prosthetic material implanted to restore a physiologic function. They were introduced decades ago as a treatment of erectile dysfunction. Infection and/or erosion associated with placement of any prosthetic material are feared complications and the standard treatment is its prompt removal. An option, termed a salvage (or rescue) procedure, is cleansing the wound with a series of antiseptic solutions and replacing a new prosthesis during the same procedure. The other alternative is to return at a later date to replace the implant.

Table 1 - Efficacy of the artificial sphincter AMS 800 in different series in literature.

Author	Year	Number	Follow-up (years)	Continence rate (%)
Marks; Light, (6)	1989	37	3.0	94.5
Montague et al., (7)	1992	166	3.2	75.0
Perez; Webster, (8)	1992	49	3.7	85.0
Light; Reynolds, (9)	1992	126	2.3	96.7
Martins; Boyd, (10)	1995	28	2.0	85.0
Fleshner; Herschorn, (11)	1996	30	3.0	87.0
Mottet et al., (12)	1998	96	1.0	86.0
Trigo-Rocha et al. (4)	2008	40	2.5	90.0

Table 2 - Complications of the artificial sphincter AMS 800 in different series of the literature.

Series	Year	Number	Infection (%)	Erosion (%)	Mechanical failure(%)
Gundian et al. (13)	1989	117	2.5	7.0	16
Marks; Light (14)	1989	16	5.4	8.1	NR
Litwiller et al. (15)	1996	65	6.0	3.1	NR
Singh; Thomas (16)	1996	28	10.0	0.0	NR
Elliot; Barrett (17)	1998	160	1.8	1.0	9
Trigo-Rocha (4)	2008	40	2.5	5.0	5

However, the latter approach is associated with technical difficulties for insertion the implant mainly due to local fibrosis. Most patients elected the salvage approach because they were highly motivated to continue sexual activity obtained with the implant placed initially. Mulcahy first described the salvage procedure for penile implant infection. His objective was to avoid difficult revision surgery, penile shortening and patient discomfort (6). Success rate of this procedure could be high as 84% (7). In patients with postoperative purulent penile prosthesis infection and no evidence of systemic infection, a conservative "local rescue" without explanation was also described. These authors employed a conservative treatment strategy by local and systemic application of clindamycin before resorting to surgical exploration with or without salvage procedures (8). Following the same principles, a group described 8 patients with an infected artificial urinary sphincter who underwent a total of 9 salvage operations. In a 33 month mean follow-up, 7 patients were free of infection with a functioning artificial urinary sphincter. In one patient, the system was removed 16 months later secondary to urethral erosion. They concluded that salvage and immediate new implantation of an infected, non eroded single or double cuff artificial urinary sphincter appears to be a valid option with 87% overall success rate. These authors also pointed out that an associated inflatable penile prosthesis does not prohibit simultaneous salvage of the two devices (9).

However, these authors did not try salvage procedure in any patient with sphincter erosion. There are in the literature two cases describing cuff erosion left without treatment (10). However, we believe our case is unique because our patient had true pump sphincter erosion and was successfully treated by a conservative surgical procedure based on cleaning and repositioning the pump.

DISCUSSION AND FUTURE PERSPECTIVES

We report the first case of sphincter pump erosion treated without removing or replacing the sphincter. When we decided to maintain the sphincter, we have considered the local and systemic conditions of the patient. The decision was taken together with the patient who was aware of the risks associated with the presence of a potentially infected sphincter. As we have learned from infected penile prosthesis (6), the conservation of the implant after rinsing it with antibiotics may be a good treatment alternative with more than 80% good results (7). Salvage surgery can also be considered for infected sphincter without erosion (10).

Take home message

Surgical treatment without sphincter removal can be an option for patients with eroded sphincters. The patient must not present signs of systemic infection and should have good local conditions. Larger series adopting this approach in select cases are needed to validate this alternative.

CONFLICT OF INTEREST

Flavio T. Rocha, MD - Surgical Preceptor Boston Scientific

Jean Felipe Prodocimo Lesting - None declared.

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Extrarenal Angiomyolipoma: differential diagnosis of retroperitoneal masses

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INTRODUCTION

Angiomiolipomas (AML) are benign mesenchymal tumors of unknown origin, that consist of mature adipose tissue, muscle fibers and blood vessel with thickened wall (1).

Renal AMLs represent 1% of renal tumors. However, extra-renal AMLs are extremely rare, and 60 cases have been described. Most extra--renal AMLs were observed at liver (18 patients) and at retroperitoneum (16 cases) (2). We report a retroperitoneum extra-renal AML.

CASE REPORT

A fifty-one years old man with right lumbar pain for one day was submitted to computer tomography that showed an incidental left retroperitoneal nodule, in close contact to ipsilateral adrenal gland.

Magnetic resonance confirmed the presence of a heterogeneous nodule, close to left adrenal, hypervascularized, with sparse focus with loss of signal in sequences with fat saturation, with approximately 2.4x2.1cm (Figures 1 and 2). Blood analysis excluded a functional adrenal tumor.

The lesion was excised by transperitoneal laparoscopy without complications, and it was diagnosed a mesenchymal lesion compatible to AML, confirmed by immune-histochemical assay (Table-1 and Figure-3).

DISCUSSION

AMLs are mainly asymptomatic incidentalomas. However, it was reported spontaneous

Figure 1 - Magnetic ressonance with axial T1WI image in phases before contrast (A), arterial (B), Portal (C) and Equilibrium (D), showing a heterogenous nodule, hypervascularized, with peripheral progressive highlight due to contrast at the retroperitoneum, measuring 2.4x2.1cm.

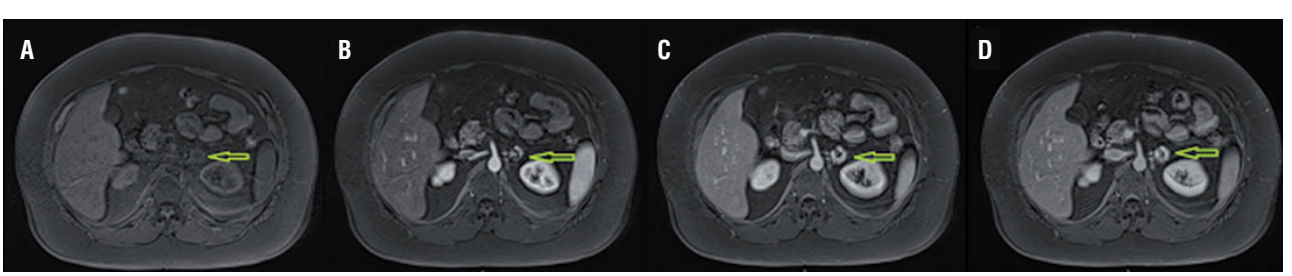


Figure 2 - Magnetic resonance images (ECO Gradient sequences GRE) T1W1 inside and outside of phase (A and B) and in T2 with and without fat suppression (C and D); they show sparse areas of signal loss corresponding to lipomatous foci.

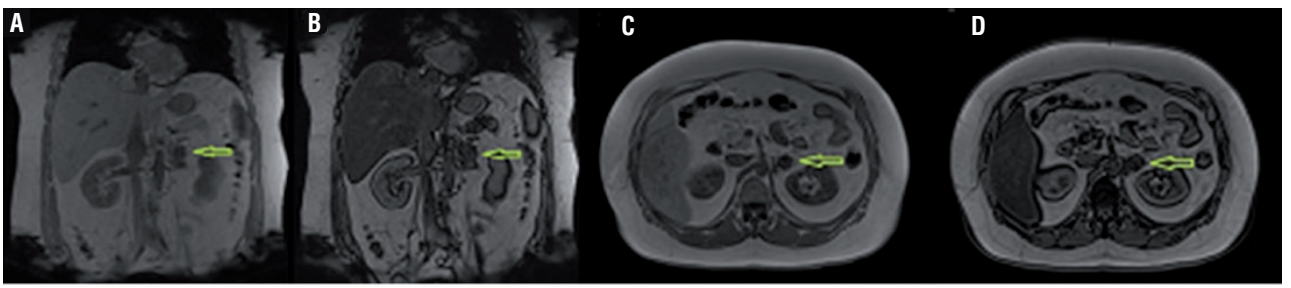


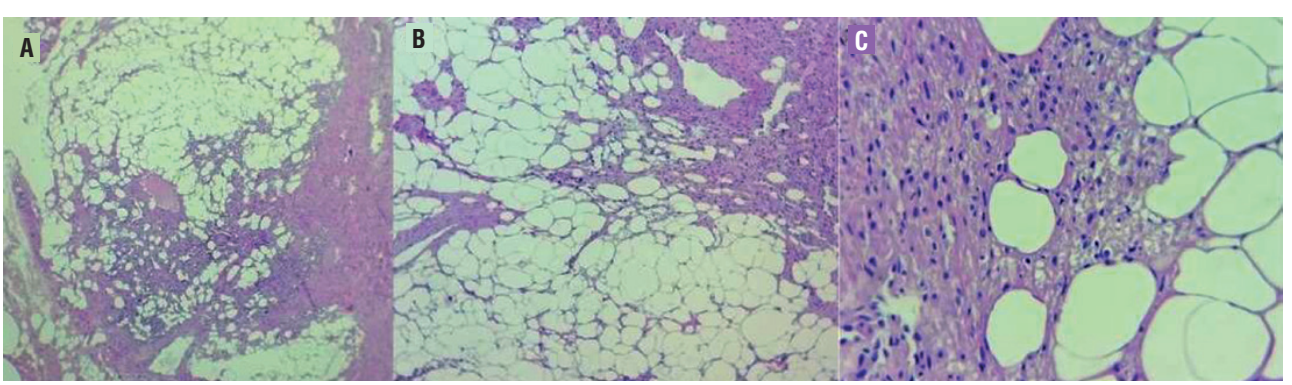
Table 1 - Immuno-histochemical results that confirm angiomiolipoma.

ANTIGEN	RESULT
HMB45	Reactivity in rare cells
Melan A	Negative
CD34	Positive
Smooth muscle actine	Positive

represent most of retroperitoneal sarcomas adjacent to adrenal gland that can be confused to myelolipoma, particularly in well-defined lesions such as the one here described (7). Other possible diagnosis include lipomas, lymphoma, adenocarcinoma metastasis and germ cell tumors, extra-gonadal dermoid cyst, hibernomas and lipoblastomas, among others (8).

Percutaneous biopsy may be inconclusive; therefore, treatment of choice must be exci-

Figure 3 – A) triphasic tumor, including mature adipose tissue, blood vessels with thickened wall and smooth muscle cells; B) component of elongated smooth muscle cells irradiating from gibbous vessels walls, permeating adipose tissue; C) angiomiolipoma, interface between mature fat cells and smooth muscle cells without atypia.



bleeding (particularly in tumors with >4cm diameter), thromboembolic events and compression of adjacent structures (3-6). Also, the risk of malignization of such tumors is unknown.

Most reported retroperitoneal AMLs include symptomatic and big tumors (2); the present tumor was a small incidental lesion.

Image exams with presence of macroscopic fat are not conclusive, since liposarcoma

sion, preferably by minimally invasive technique. In the present case, lesion excision allowed histologic confirmation, preclude follow-up with image exams and had low morbidity to patient.

It is not uncommon the need of immune-histochemical exams for diagnosis, due to histologic similarities with other tumors, such as liposarcoma, leiomyoma and lipoma (9).

CONFLICT OF INTEREST

None declared.

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Extensive renal sinus lipomatosis in xanthogranulomatous pyelonephritis simulating liposarcoma

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ABSTRACT

Renal replacement lipomatosis is a condition characterized by varying degrees of renal parenchymal atrophy and perirenal fibrofatty proliferation secondary to chronic inflammation such as xanthogranulomatous pyelonephritis. In severe cases, imaging findings can be misdiagnosed as retroperitoneal liposarcoma.

CASE PRESENTATION

A 63-year-old man was admitted to the hospital with generalized weakness, fever and weight loss for 6 months. Blood tests showed a creatinine level of 5.29mg/dl, an urea of 169mg/dl, a C-reactive protein of 297.7mg/L and urinalysis with leukocyturia.

Plain abdominal radiograph demonstrated right renal staghorn calculi (Figure-1). Computed tomography (CT) images showed obstructive stone, dilated calyces and renal parenchymal atrophy with exuberant fibrofatty proliferation (Figures 2 and 3). Final diagnosis was xanthogranulomatous pyelonephritis with extensive lipomatosis.

DISCUSSION

Renal chronic inflammation from several etiologies may induce renal parenchymal atrophy and proliferation of inflammatory and fatty cells. In severe cases of fatty proliferation and renal atrophy, the term renal replacement lipomatosis (RRL) can be used (1-4).

Xanthogranulomatous pyelonephritis (XGP) is a form of chronic inflammation, characterized by an obstructive staghorn calculous, hydronephrosis and renal atrophy (1-4). On pathology, there is destruction of renal parenchyma and replacement by lipid-laden macrophages (xanthoma cells) associated to other inflammatory cells, including plasma cells, leukocytes, and histiocytes (1-4).

Typical symptoms are nonspecific, such as flank pain, fever, fatigue, weight loss and dysuria. A palpable flank mass may be detected on physical examination. Leukocytosis and anemia are common laboratory findings and urine culture may identify Escherichia coli, Proteus mirabilis, Staphylococcus aureus, Klebsiella or Pseudomonas (4-6).

Plain radiography may demonstrate a large staghorn calculus, renal contour enlargement and, in advanced disease, obscuration of ipsilateral psoas margin (1, 5). Ultrasound usually depicts renal enlargement with dilated calyces and parenchymal destruction, renal stone and staghorn calculus (1, 4). In RRL, lipomatous tissue from renal sinus appear as an hyperechoic mass, indistinguishable from a primary retroperitoneal mesenchymal tumor (5).

Despite the findings on plain radiography and ultrasound, CT remains the best imaging

Figure 1 - Abdominal radiography demonstrates staghorn calculus in right kidney.

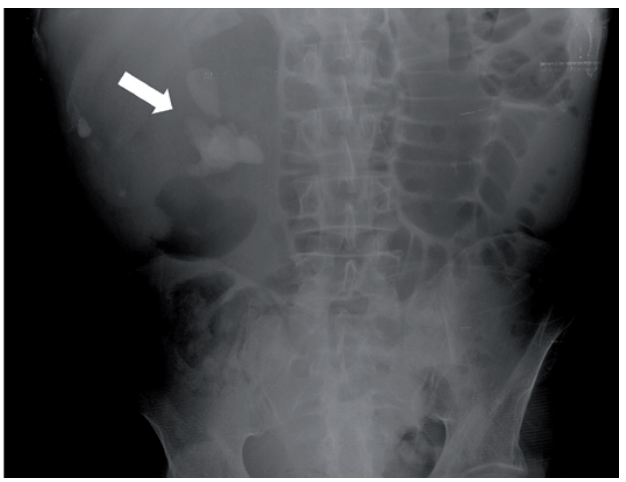


Figure 2 - Axial post-contrast CT images show obstructive stones, dilated calyces and renal parenchymal atrophy on the right kidney. Exuberant fibrofatty proliferation in renal sinus, indicating renal replacement lipomatosis (A, B and C).Calyceal dilatation with a multiloculated aspect similar to the toe pads of a bear's paw in XGP (D).

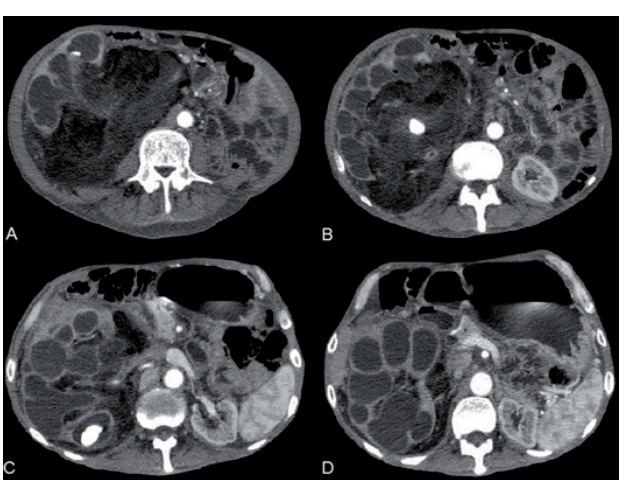
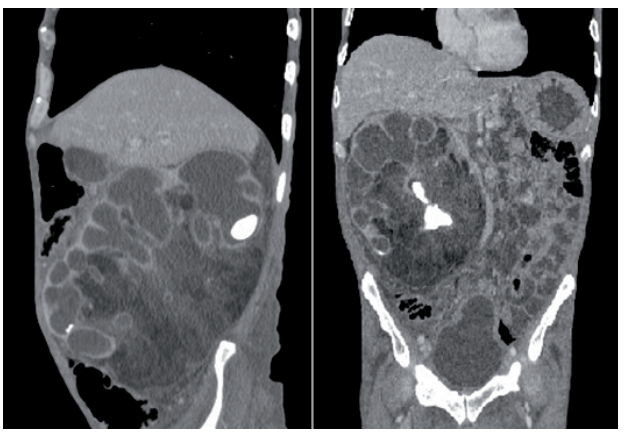


Figure 3 - Sagittal and coronal CT images show calculi, dilated calyces and renal parenchymal atrophy and exuberant fibrofatty proliferation.



modality to evaluate these conditions, not only for diagnosis but also to evaluate extension and surgical planning. An obstructive pelvic stone and calyceal dilatation with a multiloculated aspect can be observed, similar to the toe pads of a bear's paw in XGP. This appearance reflects an atrophic renal parenchyma replaced by enlarged calyces with thick content (2, 4, 6-8).

In the RRL, besides the findings of XGP, there is extensive fatty tissue within the renal sinus, hilum and perinephric space (2, 5). Those characteristics are shared with retroperitoneal liposarcoma, a rare tumor that arises from the retroperitoneum that may occur in this region, and may impose diagnostic dilemmas (9). Since in RRL and XGP there is minimal or absent renal function on the affected kidney, nephrectomy is usually the treatment of choice (10).

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Saphenous–sparing laparoscopic inguinal lymphadenectomy

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ABSTRACT

Introduction: Inguinal lymphadenectomy is an integral part in the management of penile cancer. Video endoscopic inguinal lymphadenectomy (VEIL) is emerging as a minimally invasive treatment to reduce postoperative complications.
Materials and Methods: 62 years old man underwent glansectomy for a squamous cell carcinoma (pT1b). At the physical examination one left inguinal lymph node was detectable (cN1). The chest-abdomen-pelvis CT was negative for metastasis. A 10-mm optical trocar and two 5mm operating trocar were placed. The optical trocar was placed in the apex of Scarpa's triangle after a skin incision and after the creation of a subcutaneous space by blunt finger dissection. The pCO2 was 8-10mmHg. The surgical technique involved the removal of superficial lymph nodes according to the scheme described by Deseler and of the deep lymph nodes. Sparing main venous structures and closing lymphatic vessels is important to reduce post operative complications. At the end of the procedure, a suction drain was placed per side.
Results: Operative time was 90 minutes per side. Drains were removed on the seventh postoperative day. Hospital stay was 8 days and no postoperative complications occurred. The total number of nodes removed was 16 (8 per side) with 2 superficial positive nodes on the left side.
Conclusion: ILND is burned by a high complication rate. VEIL provides a less invasive approach and a saphenous-sparing technique ensures a lower complication rate, reducing lymphorrhea, skin necrosis and wound complications (1-3). In experienced laparoscopic hands, VEIL is a safe and effective treatment.

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CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Surgical repair in case of covered exstrophy of bladder with complete duplication of lower genitourinary tract and visceral sequestration

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PURPOSE

Management of complete lower urinary tract duplication remains a major challenge. We present a video-case of covered exstrophy of bladder with complete duplication of lower genitourinary tract and visceral sequestration.

MATERIALS AND METHODS

An eleven year old female child presented with abnormal structure over the genital area since birth and continuous urine leak. Patient had history of premature birth at 28 weeks of gestation. Anus was anteriorly displaced in exstrophy complex. Labia majora and minora were divergent and clitoris was bifid. Two normal vaginas were present on both sides lateral to genito- urinary complex structure. Patient had single urethral meatus which opened above right vaginal orifice.

MRI pelvis was suggestive of pubic diastasis with duplication of urinary bladder, uterine didelphys with two ovaries and two vaginas. Excretory urography confirmed duplication of urinary bladder with opening of right ureter into right bladder and left ureter into left bladder. Patient had left sided hydro-ureteronephrosis and no demonstrable outlet. There was herniation of right urinary bladder through anterior abdominal wall defect and urethra was originating only from right bladder.

Surgical procedure consisted of joining of both the bladders and dissection of urethra. Decision to excise the urethra was taken as there was no demonstrable bladder neck sphincter; Mitrofanoff procedure was done for drainage. External genitalia reconstruction consisted of clitoroplasty, mons reconstruction and labioplasty. Sequestered part was excised; pubic bone defect was closed with raising rectus sheath flap.

CONCLUSION

Comprehensive preoperative imaging and meticulous planning is needed for management of rare and complicated lower urogenital anomalies. Surgical procedure achieved all of the preoperative goals in this case. Quality of life improved with cessation of continuous dribbling and improved cosmesis of external genitalia. Functional outcome improved with drainage of left side urinary system into the unified lower urinary tract.

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VIDEO SECTION

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Laparoscopic transperitoneal repair of retrocaval (circumcaval) ureter

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INTRODUCTION

Retrocaval ureter occurs because of the persistence of the posterior cardinal veins during embryologic development; as an anomaly of inferior vena cava. This can cause varying degrees of ureteral obstruction and surgical intervention is often necessary. We herein report a case of laparoscopic transperitoneal repair of retrocaval ureter.

PATIENT AND METHODS

A 36-year-old female patient presented with recurrent attacks of flank pain of two years duration. Ultrasound showed right hydronephrosis and dilatation of proximal ureter. Intravenous urography showed right grade 2 hydronephrosis, and the "reverse J" shape of the collecting system suggested retrocaval course of the ureter. Magnetic resonance urography showed grade 2 obstruction due to hooking of the proximal ureter around the inferior vena cava. Laparoscopic transperitoneal retrocaval ureter repairment was planned for our patient. Patient was placed under general anesthesia. A Foley catheter No. 16 Fr size was inserted. After pneumoperitoneum was established in right flank position, three 10 mm trocars were placed including one camera port. Retroperitoneal region visualised through the incision of toldt line and medialisation of the ascending colon. 5 mm trocar was placed for convenience to retraction and dissection. After exposing the retroperitoneum, the ureter was identified coursing posterior to the inferior vena cava. The dilated ureter was identified and dissected out up to the lateral border of IVC. The lower ureter also was mobilized in the inter-aortocaval region. The retrocaval portion was also dissected out and mobilized. The proximal ureter was divided at the ureteropelvic junction and transposed anteriorly. The proximal ureter was spatulated and prepared for ureteropelvic anastomosis. A stay suture was taken from the proximal ureter, which stabilized the ureter. The posterior side of ureteropelvic anastomosis performed with a 4.0 vicryl suture in a continuous fashion. The anastomosis was continued on the anterior side with a new suture. A 4.8 French 26 cm double j stent was placed through the 14 French Amplatz dilator before completing the anastomosis. Amplatz dilator was passed through the right 10mm trocar so that the distal portion of the double j stent passed therethrough could be more easily manipulated within the surgical field. We have reduced the stent placement time to a minimum with this necessary method, which was not previously described in the literature. A closed suction drain was placed on the site and the operative site was not retroperitonealized. The surgery was uneventful, with no operative complications or evidence of intra-abdominal bleeding.

According to the publications in the literature, it is noted that some of the urologists place a double J stent before the procedure. Preoperative ureteral stenting may facilitate ureteric identification but we believe that the double j stent inside an ureter may limit the mobilization of an ureter, especially the retrocaval portion.

RESULTS

The duration of the surgery was 75 minutes. The amount of bleeding was 28mL. On the postoperative 2nd day, the urethral catheter was removed and the patient was discharged on the third day postoperatively. Stent removal was done on the 3rd postoperative week and retrograde pyelogram showed normal ureter. Post-operative follow up with ultrasound showed that hydronephrosis had regressed.

CONCLUSIONS

Laparoscopic transperitoneal repair of retrocaval ureter is useful and feasible, with minimal invasiveness and an early post-operative recovery. Laparoscopic transperitoneal procedure may be preferable for retrocaval ureters.

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VIDEO SECTION

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Retroperitoneoscopic nephrectomy for huge autosomal-dominant polycystic kidney disease using morcellator

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ABSTRACT

Introduction and Objectives: Nephrectomy is occasionally required due to severe extra-renal symptom(s) such as dyspepsia in patients with autosomal dominant polycystic kidney disease (ADPKD), wherein a large incision is required for specimen extraction. Considering problems such as hernia, wound dehiscence, incidental bowel injury, and poor wound healing in such cases, we would like to present retroperitoneoscopic nephrectomy and morcellation of the kidney as an ideal minimally invasive technique.
Materials and Methods: A 53-year-old man who was undergoing hemodialysis for 6 years due to ADPKD visited the outpatient clinic with a complaint of severe dyspepsia. Kidney length (long axis) was greater than 28 cm. Nephrectomy was the last option to restore his digestive system which was mechanically compressed by an extremely enlarged polycystic kidney. Retroperitoneoscopic nephrectomy was performed using 3 ports. When it was difficult to continue the dissection due to limited space, large cysts were punctured and aspirated to create additional working space. The specimen was extracted by a morcellator (KARL STORZ GmbH & Co. KG, Tuttlingen, Germany) introduced through a 12mm trocar.
Results: Operating time was 230 minutes, wherein the time for morcellation was 52 minutes. No additional incision was required for specimen extraction. He underwent hemodialysis on post-operative days #1 and #3. He was discharged on post-operative day #4 (total hospital stay was 6 days.). Dyspepsia dramatically improved without post-operative complications.
Conclusions: Retroperitoneoscopic nephrectomy is feasible for treatment of ADPKD. By using a morcellator, an additional incision is not required and wound complication would not occur.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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Re: Gaseous bladder tamponade secondary to emphysematous cystitis

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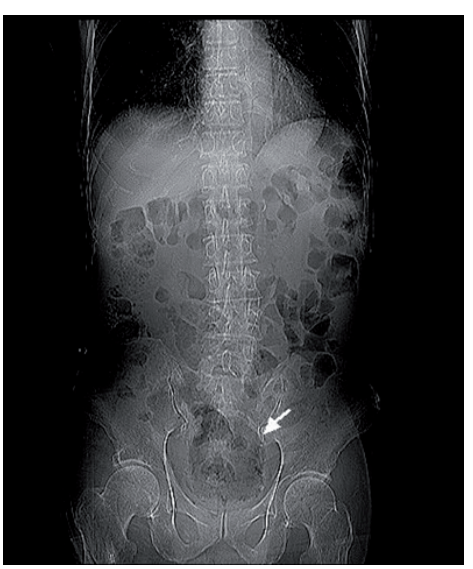
To the editor,

Recently, Yang et al. (1) published the abdominal computed tomography (CT) images showing diffuse gas within the bladder wall and a prominent air-fluid level as the typical manifestation of emphysematous cystitis. However, it's not only involved in the bladder wall but also in the bladder lumen (2, 3). We hereby present a case of gaseous bladder temponade causing obstructive uropathy - a rarely severe complication of emphysematous cystitis.

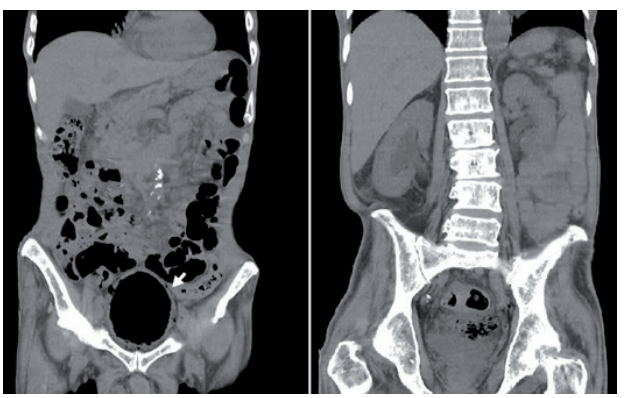
Our patient is a 81-year-old man who presented to the emergency department with 2 days of history of fever, progressed low abdominal distention and decreased urine output. He had type 2 diabetes mellitus and flaccid neurogenic bladder with long-term indwelling Foley catheter for the preceding two years. Laboratory studies revealed bacteriuria, leukocytosis, an elevated C-reactive protein level, high fasting blood glucose (302mg/dL), and an elevated creatinine level (2.05mg/dL). Radiography of the kidneys, ureters, and bladder revealed a low density over the whole bladder area and linear collection of gas along bladder wall (Figure-1). Abdominal CT was subsequently arranged, which showed gas tamponade in the bladder with bilateral obstructive hydronephrosis (Figure-2). A new Foley catheter was changed, and bladder irrigation was performed to extract pus and gas. He was treated with broad-spectrum antibiotics and strict blood sugar control. Both blood and urine cultures grew Klebsiella pneumonia. He responded with defervescence and recovery of renal function (creatinine=1.39mg/dL) after a full course of antibiotics treatment.

Figure 1 - Radiography of the kidneys, ureters, and bladder revealed a low density over the whole bladder area and linear collection of gas along bladder wall (arrow).



Emphysematous cystitis is an uncommon disease characterized by the presence of air within the bladder wall and lumen, and primarily observed in diabetic patients. In this

Figure 2 - Abdominal computed tomography revealed bladder tamponade with massive air accumulation in bladder lumen and bladder wall (arrow), which leaded to bilateral hydronephrosis.



case, gaseous bladder tamponade with bilateral obstructive hydronephrosis is a rarely emergency complication of emphysematous cystitis. Prompt diagnosis by radiography, broad-spectrum antibiotics, immediate drainage and intensively underlying diseases control are critical. Importantly, we suggest that all patients with long-term indwelling catheters and immunosuppression should note this rare sequela.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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Re: Dipyridamole reduces penile apoptosis in a rat model of post-prostatectomy erectile dysfunction

Shanzun Wei [1,2], Ming Ma [1,2], Changjing Wu [1], Botao Yu [1,2], Jiuhong Yuan [1,2]

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To the editor,

We read with interest the recent in vivo research in attempt to recover erectile dysfunction after radical prostatectomy accomplished by Omer kutlu et al. (1). They apply dipyridamole treatment in animal model of cavernous nerve crush injury. While they successfully unveiled that dipyridamole reduces apoptosis indices and TGF-β1 level in corpus cavernous tissue, they failed to establish improvement in ICP value-the golden standard of erectile function.

The author reckons the short period of treatment may result in the negative ICP difference between vehicle and treatment group. As to the modelling, 15 days in current study is sufficient for nerve crush injury to induce erectile dysfunction. Mullerad et al. previous revealed that decline in ICP may be detected 3 days after BCNI surgery, but no difference was observed in 10 days and 28 days post-surgery (2). However, Chan-Ho lee et al. compared the prognoses of post BCNI treatment between 4 weeks and 8 weeks after BCNI surgery. They discovered that 8 weeks of post BCNI treatment is more beneficial in ameliorating ICP declination and reducing cavernous SMC apoptosis than the 4 weeks regimen (3).

Furthermore, another ED etiological factor followed by PR surgery is operation related neurapraxia, which may result from mechanical traction, ischemia and focal inflammation (4). The adjacency predisposes the vulnerability of cavernous nerve in the RP surgery. Whereas, the most exquisitely performed nerve sparing-PR surgery may still render the possible occurrence of neurapraxia with impaired ED episode and is up to 18-24 months (5). In the current research, 15 days of treatment in rats merely equals to a rehabilitation program of 1 year for humans. This may partially explain limited ICP restoration achieved by the author in the15 days treatment (6). And we believe that if the author has extended the treatment period, a more pronounced therapeutic effect may thus be shown.

Transperitoneal anaesthesia with ketamine and xylazine mixture is valid and consistent in each group. However, we have previously assessed the impact of anesthesia on ICP values of normal rats and discovered that ICP value in rats anesthetized with inhalation was higher than rats anesthetized transperitoneally (7). Inhalation anaesthesia is more prompt in controlling anaesthetic depth control and regulating vital signs. It did not manifest with significant different vital signs and oxygen saturation compared to transperitoneal anaesthesia in rats. Also, it is suggested that inhalation anaesthesia may lead to steadier physiological state, provide sustainable and adequate anaesthesia depth that is advantageous in achieving valid and consistent ICP value. It can also reduce the risk of anaesthesia induced casualty. Li also believes that local anaesthetic effect could not be ruled out in transperitoneally anesthetized, and this may be another factor for the lower ICP.

In conclusion, we believe if the authors extended their treatment period and switched the anaesthesia, not only they would have achieved better apoptosis index, but also would have shown

improvement in erectile functional index. For their discovery resembles to Karaguzel's research (8). Karaguezel applied dipyridamole in reducing acute penile ischemic and reperfusion injury in priapism. Though they did not focus on the dipyridamole's effect on reduce cavernous tissue apoptosis nor restoration post injury induced erectile function impairment. Both studies unveiled a promising therapeutic role of dipyridamole in reducing acute and chronic ischemic impact and disclosed a promising future of dipyridamole in urology clinic application.

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CONFLICT OF INTEREST

None declared.

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