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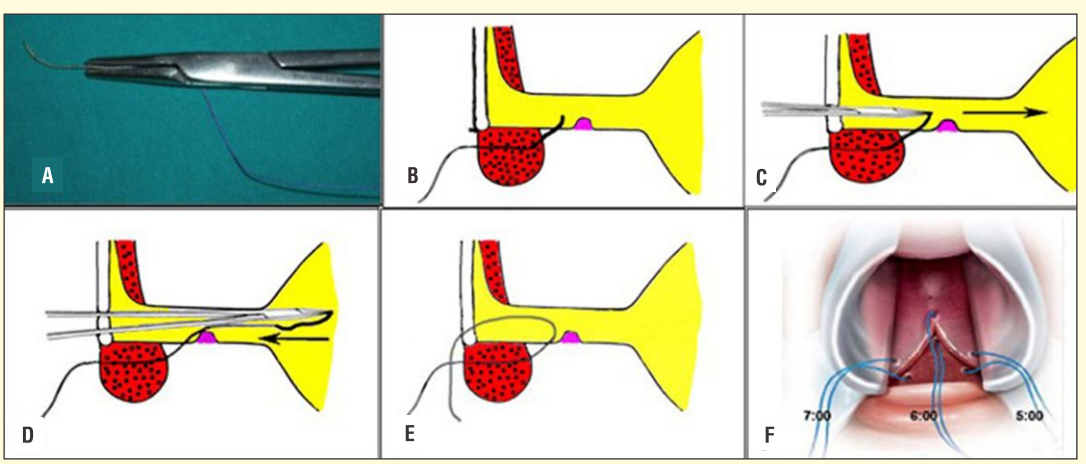

A) The j-shape needle; B) The needle is moved in front up to the verumontanu; C) The needle is pushed head into the bladder; D and E) The needle is withdrawing back; F) Three stitches are inserted at 5, 6, 7 o'clock near the veru montanu. (*page* 517)

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DISCLAIMER

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Vol. 46 (4): 496-498, July - August, 2020
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In these difficult times of COVID-19, urologic research cannot stop: COVID-19 pandemic and reconstructive urology highlighted in International Brazilian Journal of Urology

Luciano A. Favorito [1, 2]

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In times of great difficult because the Covid-19 infection the urologic research cannot stop. The July-August number of *Int Braz J Urol*, the fourth under my supervision, presents original contributions with a lot of interesting papers in different fields: Prostate Cancer, Uretral Stricture, Sexual Function, Male Incontinence, Buried Penis, Vesicoureteral Reflux, Prostate Biopsy, Kidney Transplant, Renal Cell Carcinoma, Bladder Cancer, BPH, Laparoscopy and Testicular Cancer. The papers came from many different countries such as Brazil, USA, Turkey, China, Korea, Coloumbia, Poland, Germany, Taiwan, India and Italy, and as usual the editor´s comment highlights some of them.

In the present issue we present three important reviews. Dr. Barbagli and colleagues from Italy performed in **page 511** (1) a nice narrative review about the bulbar urethral stricture treatment. This study is on the cover in this number. Dr. Barbagli is one of the most important urethral surgeons in the world and in this paper he present some tips and tricks developed along their prolonged surgical experience on the treatment of bulbar urethral strictures. Dr. Burks and colleagues from USA (2) present in **page 519** an important review about acquired buried penis (AABP). Dr. Burks shows that the management of AABP requires a combination of genitourinary reconstructive techniques and plastic surgery techniques that are unique to this condition and shows important tips and tricks for the treatment of AABP. Dr. Netto and collegues from Brazil presented in **page 523** (3) a nice paper about a consensus with practical orientation on how to evaluate and treat Vesicoureteral reflux in Brazil and addressed important recommendations on up to date choice of diagnosis evaluation and therapies. The editor in chief would like to highlight the following works too:

Dr. Porcaro and collegues from USA (4) on **page 545** evaluate the association between prostate volume index (PVI), and prostatic chronic inflammation (PCI) as predictors of prostate cancer (PCA). PVI is the ratio between the central transition zone volume (CTZV) and the peripheral zone volume (PZV) and concluded that high PVI and the presence of PCI lowered the mean rate of NPC and is associated with less aggressive tumor biology expressed by low tumor burden. PVI can give prognostic information before planning baseline random biopsies.

Dr. Demirtas and Collegues (5) from Turkey perfomed on **page 557** a interesting study about fusion prostate biopsy (FPB) and compare the pain levels in TRUS-guided standard 12-core prostate biopsy

(SPB) and MpMRI-guided FPB. The authors concluded that FPB, with a relatively higher cancer detection rate, leads to the same pain level as SPB although it increases the number of biopsy cores and involves a more complex procedure compared to SPB.

Dr. Sefik and Collegues (6) from Turkey performed on **page 566** an interesting study about the preoperative renal function on survival outcomes in patients who underwent radical cystectomy (RC) with non-continent urinary diversion (UD) and concluded that overall mortality was higher and overall survival was lower in patients with preoperative eGFR <60mL/s. More patients had preoperative hydronephrosis with eGFR< 60mL/s.

Dr. Sipal and Collegues (7) from Turkey studied on **page 575** the reasons of storage symptoms (SS) after transurethral resection of the prostate (TURP) and they studied if was a positive correlation between preoperative and postoperative SS in patients with undergoing TURP and starting early solifenacin treatment in patients with high preoperative SS would be reasonable and concluded that TURP provides significant improvement in both storage and voiding symptoms. The predictive value of the preoperative S-IPSS on postop SS is significant. These results suggest that 5 mg solifenacin succinate treatment in the early postoperative period may be beneficial for patients with high preoperative SS and may not be beneficial in others. Small prostatic volume may bode ill for postoperative SS in the patients with de novo SS.

Dr. Liu and Collegues (8) from China shows on **page 585** explore the prognostic value of obesity (measured by BMI) on Renal Cell Carcinoma (RCC) in a systemic inflammation state and concluded that in localized RCC patients, obesity was an independent protective factor for cancer specific survival and recurrence free survival in a systemic inflammation state.

Dr. Vidal and Collegues (9) from Colombia studied on **page 599** evaluated the role of baseline clinical variables associated with overall survival (OS) and toxicity of Radium 223 (223Ra) and concluded that 223Ra therapy require an adequate selection of patients to obtain the greatest clinical benefit. Low basal Hb, hight basal alkaline phosphatase ALP and bone marrow involvement were the main factors that decreased overall survival in this study. 223Ra should be considered relatively early in the course of treatment.

Dr. Kretschemer and collegues (10) from Germany shows on **page 632** a interesting study about the effect of perioperative complications involving artificial urinary sphincter (AUS) implantation on rates of explantation and continence as well as health-related quality of life (HRQOL) and concluded that postoperative infections adversely affect device survival after AUS implantation and the comparative long-term functional results and HRQOL outcomes are similar between patients with or without perioperative complications.

In this very difficult times of COVID-19 I ask everyone to read the amazing editorial of Dr. Francisco Sampaio (11) our Emeritus Editor. Dr. Sampaio in his editorial show us important aspects of the Pandemic and in this issue he have one of the most complete reports on the clinical practice of Urology in COVID-19 Pandemic times in the briliant paper by Dr. Carneiro and Collegues on page 501 (12). We hope that readers will enjoy the present number of the *International Brazilian Journal of Urology.*

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Int Braz J Urol. 2020; 46: 496-8

EDITORIAL

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Reflections on the COVID-19 Pandemic

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This editorial represents a compilation of reflections that I have made during the last few days. Now, at the invitation of the Chief Editor I would like to share them with the urological community.

After the Covid-19 pandemic recedes, humanity will need to rethink their way of living. Everyone is vulnerable. The virus doesn't distinguish: the rich or the poor, the important or the ordinary people. Everyone now realizes there is no point in having money or residences in three or four different countries or on various continents in an attempt to escape the crises; they can't escape, the world becomes too small. Everyone is at risk: politicians, ministers, governors, prime ministers, presidents, princes, the rich and the poor ... no one can escape the virus, and at this moment, just being able to breathe well is a blessing.

Urologists are no longer operating; elective surgeries have been postponed, outpatient clinics have suspended consultations, and in many countries urologists have already left the specialty and are dedicating themselves to patients with Covid-19. The healthcare systems of many countries are collapsing and the percentage of doctors and other health professionals who have become contaminated is very large.

I hope that when this pandemic passes, all countries will start to worry about the many other infectious diseases, which have been plaguing mankind for years, even though treatments and/or vaccines exist for many of them. Why has the world never been so concerned with yellow fever, rabies, measles, meningitis, cholera, malaria, whooping cough, rotavirus, shigellosis, hepatitis B and tuberculosis, as well as many other neglected contagious infectious diseases that kill so many? As example, tuberculosis alone kills 4,500 people a day in the world. Nevertheless, these diseases are not pandemics.

We are in panic because Covid-19 is very contagious and does not discriminate. Everyone can get sick and very quickly fill the hospitals, and then, no one, not even the rich and powerful can access the lifesaving care they desperately need. Covid-19 also causes an enormous economic chaos, affecting all social classes, no one is immune. Since Covid-19 does not distinguish, and has no treatment, the World is now in a panic.

At this moment we still don't know how to deal with this disease. Covid-19 has no vaccine and no effective proven treatment. It seems that the only effective way to reduce the devastating effects of Covid19 on healthcare systems is social distancing and isolation. The problem is social distancing also leads to economic collapse and it is difficult to recover from the effects of this form of treatment.

In the meantime, scientists around the world are desperately searching for effective vaccines and treatments for this devastating disease and we are all hoping that they will soon emerge to mitigate this pandemic. The world needs to work together to both defeat is as well as finding a solution.

At this point, we must emphasize the following advice to the population: **stay at home**. The fewer people who became ill in the short term, the better the health systems will be able to care for patients with Covid-19 in serious condition, thus increasing the chance of survival. Be well.

Respectfully,

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LECTURE

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Impact of the COVID-19 Pandemic on the Urologist's clinical practice in Brazil: a management guideline proposal for low- and middle-income countries during the crisis period

Arie Carneiro [1, 2], Marcelo Langer Wroclawski [1, 3], Bruno Nahar [4], Andrey Soares [5, 6, 7], Ana Paula Cardoso [5], Nam Jin Kim [8], Fabricio Torres Carvalho [9, 10]

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ABSTRACT

This letter to the Editor aims to provide suggestions and recommendations for the management of urological conditions in times of COVID-19 crisis in Brazil and other low- and middle-income countries.

It is important to highlight that one of the main characteristics of this pandemic is the oversaturation of the health system capacity, mostly due to a high demand for personal protective equipment (PPE), Hospital/ICU beds, as well as ventilators. In places with limited resources and where the health care systems are already saturated, such consideration is even more worrisome.

Therefore, most worldwide authorities are recommending to avoid, as much as possible, patient's elective visits to hospitals, as well as a judicious use of the operating room in order to mitigate the strain put on the health system. While efforts should be directed to the care of COVID-19 patients, other conditions (especially urgencies and oncological cases) must continue to be assisted.

Thus, through a panel of experts, we have prepared a practical guide for urologists based on the recommendations from the main Urologic Associations, as well as data from the literature to support the suggested management. We will try to follow the standard guideline recommendations from the American Urological Association (AUA) and European Association of Urology (EAU), with the aim of pursuing the best outcomes possible. However, some recommendations were based on the consensus of the panel, taking into consideration the reality of developing countries and the unprecedented situation caused by the COVID-19 crisis.

Most importantly, all recommendations on this manuscript are based on the expectancy of a maximum 3-month duration of the crisis. If this period shall extended, these recommendations will be revised and updated.

The format of the text will be given through questions and answers.

How much is the pandemic by COVID-19 impacting the clinical practice of the urologist?

Similar to other specialties, the pandemic has drastically changed the routine of the urologists. Elective clinic visits are being canceled, postponed or, in some situations, replaced by remote care through telemedicine, recently regulated and temporarily authorized by the Brazilian Ministry of Health (1).

We believe that tele-screening, test reviews and follow-up evaluations that do not require physical examination are the ideal situations for this type of care, especially when the patient is in the high-risk group and must be socially isolated (2).

In regard to surgeries, all postponable procedures must be rescheduled, in order to reduce the exposure of the surgical team and the patient to a potential contamination. Furthermore, cancelation of surgeries collaborates with social isolation and save resources (such as PPEs) for the care of patients with COVID-19 infection. The main question is how to define which operations can really be postponed, especially in urologic oncology, without interfering with the patient's outcomes.

What general care should be taken in any type of surgery during this period?

The most important recommendation at this point is that elective surgical procedures should be postponed. The diagnostic, therapeutic and human resources of the Health Care facilities must be available to fight the pandemic(3). Some considerations should be made:

a) We must consider all cases as suspect, until proven otherwise. Ideally, every case should be tested by rRT-RNA-CRP for SARS--CoV-2 48 prior to surgery, but unfortunately this is not feasible in most developing countries. Negative confirmed cases should be kept in a separate environments.

b) Surgeries for COVID-19 negative patients should ideally be performed in a surgical center different from the location where patients with positive COVID-19 are being treated. If it is not possible to separate an entire surgical block, we suggest designating specific rooms for the care of patients with COVID-19 that will not be used for regular cases.

c) A trained and dedicated multidisciplinary team should be available for the management of suspected and confirmed patients for COVID-19. It is preferable that this team does not assist COVID-19 negative cases.

d) Whenever possible, we should prioritize surgeries with local anesthesia or spinal blockade.

e) Always obtain a consent form, as recommended by the Brazilian Society of Medical and Bioethics Law. Patients are at risk of contracting COVID-19 infection during their hospital stay and major surgeries in asymptomatic infected patients during the incubation period appear to predict worse outcomes, with a mortality rate up to 20% (3).

f) After the procedure, COVID-19 positive patients should be admitted to the designated areas for suspected and / or confirmed patients with COVID-19, if the institution in question provides such area.

Should we always perform pre-surgical screening?

- If available, we recommend testing all patients for rRT-RNA-PCR for SARS-CoV-2 48 hours before performing the procedure.

- If it is impossible to test everyone with the resources available, all cases should be considered suspect.

In case of surgery, what is the proper vestment and PPEs for health care providers?

For everyone in the room: caps, personal protective glasses, N95 mask (PFF2 or PFF3), protective gowns for contacts, procedure gloves and shoe covers. For those who will perform procedures: cap, personal protective glasses, face shield, N95 mask (PFF2 or PFF3), sterile waterproof apron, sterile gloves, shoe covers and waterproof disposable boots whenever secretions (when urine, stool or blood are expected, such as in endourological procedures) are expected.

- In the setting of N95 masks rationing, the face shield is important in order to prevent soiling of the mask, that can be further reutilized.

- Increased care should be taken when handling patient's stool. Studies have shown that even in patients with negative airway CRP, the clearance of the the viral RNA is longer in the stool (4). Thus, surgeons should take extra precautions with surgeries that include bowel manipulation and trans-rectal prostate biopsies.

What is the correct way of surgical vesting in COVID-19 positive cases?

a) On the corridor:

- Hand Hygiene;
- Put on the N95 mask and goggles or face shield for anesthetists, in the case of intubation.
- Perform surgical hand antisepsis.

b) In the lobby

- Put on a surgical gown.
- Put on sterile gloves (Surgical team);
- The anesthesiologist should use 2 pairs of gloves and after intubation the second pair should be changed as soon as possible.

What is the correct order to remove the surgical PPE?

a) Inside the room:

- Remove gloves;
- Hand hygiene;
- Remove disposable gown;
- Hand hygiene.

b) Outside the room: (Leave a side table with an Oxivir® drum and procedure gloves).

- Remove glasses;
- Remove the N95 mask and place it in an identified plastic bag;
- Remove the cap;
- Hand hygiene;
- Put on procedure gloves and clean and disinfect the glasses and support surface (Use disinfectant detergent - Oxivir® or Optigerm ®);
- Remove the gloves;
- Hand hygiene. After removing protective equipment, remember not to touch your hair or face before hand washing.

What special care should we take in laparoscopic / robotic surgery?

Some studies have suggested transmission of some pathogens (coryneobacterium, papillomavirus and HIV) by the pneumo peritoneum through the release of smoke generated by the laparoscopic electrocautery (5-7). A parallel situation may be extrapolated to the coronavirus.

Therefore, additional care in these procedures must be performed:

a) As mentioned earlier, it is important to test all patients before the procedure, if possible.

b) Additional protection in relation to aerosol dispersion: Always keep materials clean, assistants must have additional care when placing and removing trocars, do not use trocars with air leakage, avoid using monopolar energy and give preference to bipolar, keep settings of the electrocautery to minimum in order to reduce smoke formation.

c) Handling of pneumoperitoneum: keep it as low as possible, minimizing the Trendelenburg as much as possible. If possible, use devices that are able to aspirate and filtrate the smoke from the pneumoperitoneum.

d) During disinflation, the CO2 gas and smoke should be captured with an ultra-filtration system. A disinflation mode should be used on your insufflator if available.

e) If available, use filters on vacuum cleaners, there are different models and brands.

f) Use drains only when extremely necessary because post-operative care in the presence of organic fluids demand extra-caution and additional PPE.

g) Favor the open approach in cases where minimally invasive surgery has not shown considerable benefit.

What general care should urologists take during the pandemic?

When should we go into isolation?

Urologists, like other physicians, should be isolated only when they become suspected or confirmed cases of COVID-19. In suspicious cases, the SARS-CoV-2 RT-RNA-CRP should be collected and physicians should be kept isolated until the result.

Physicians with the following symptoms should be considered highly suspicious for COVID-19: fever, respiratory symptoms (cough, runny nose, nasal obstruction, sore throat, shortness of breath, loss of smell), in addition to body aches, fatigue, diarrhea and nausea (8).

When should we perform the test?

Healthcare professionals should always be tested when symptomatic.

How long is quarantine recommended?

The duration of the quarantine is 14 days, starting on the day of onset of symptoms. Individuals should be asymptomatic at the end of this period. Otherwise, they should remain isolated until symptoms are resolved, and only return to activities 72 hours after the resolution of all symptoms. The Center for Disease Control and Prevention (CDC-USA) recommends the utilization of RT-RNA-CRP for control and only release physicians to work after a negative result. However, due to the lack of tests in most of the country, this is not mandatory by the Brazilian Ministry of Health (9).

In general urology, which surgeries should not be postponed?

In cases of patients with urinary lithiasis

All surgeries to treat urolithiasis should be suspended, unless these are emergencies.

In the presence of ureteral lithiasis associated with fever or other signs of infection, there is an absolute indication for antibiotic therapy and urinary drainage. Preferably, we opted for the passage of a ureteral stent (i.e double J stent) under spinal anesthesia (or even with local anesthesia). As an alternative, bedside ultrasound percutaneous guided nephrostomy might be considered in centers with the necessary expertise(10).

In addition to lithiasis associated with urinary tract infection, ureteral obstruction in a solitary kidney or bilateral ureteral obstruction, acute impairment of renal function and pain refractory to clinical treatment should not be postponed. Unlike other recommendations(11), our position is that, once the surgical procedure is indicated, we should be as resolutive as possible, in order to reduce the number of visits to the hospital for new surgeries to the emergency department. Thus, instead of just draining the urinary tract, our tendency is to perform ureterolithotripsy whenever possible and safe, keeping the double J stent with a string externalized by the urethra to be removed on an outpatient basis.

The remaining cases of renal colic should preferably be managed clinically, with medical expulsive therapy and pain control. However, it is important to note that, invariably, cases initially conducted in this way may evolve into emergency situations, such as those previously mentioned.

Patients who are already with a double J stent may remain with the stent for as long as possible. Surgery may be indicated in cases of extreme ureteral stent discomfort. Otherwise, clinicians must keep strict control of all cases in order to avoid the forgotten double J syndrome.

In cases of patients with benign prostatic hyperplasia

Patients with benign prostatic hyperplasia should not be operated at this time of a pandemic, unless they develop complication that will require hospitalization and possible surgery, such as massive hematuria and clot retention. In this scenario, we believe that the evacuation of clots and / or cauterization of the prostate should already be accompanied by resection, vaporization or endoscopic enucleation of the prostate (12).

In all other cases, even if there is urinary retention, we recommend postponing the procedure. If necessary, indwelling urinary catheter placement or percutaneous cystostomy with local anesthesia are indicated for preservation of renal function(13, 14).

In cases of patients with hematuria

The investigation of hematuria through imaging tests during COVID-19 pandemic should be limited to cases of macroscopic hematuria, especially if there are clots or hemoglobin decrease. Greater attention should be given to patients at higher risk for urothelial carcinoma, such as men, over 50 years of age and with a history of smoking and exposure to known carcinogenic agents.

The gold standard test for investigation of the upper urinary tract is uro-tomography, but in times when we need to consider the use of resources, ultrasound could potentially be used since many imaging services are overloaded due to the frequent indication of thoracic CTs for the diagnosis and follow-up of patients with Sars-Cov-2. These data are extrapolations from recent evidence that ultrasound could replace tomography in the investigation of microscopic hematuria (14). However, once the outbreak is resolved or if the resource is available, uro-tomography should be performed.

Regarding the lower urinary tract, flexible cystoscopes are not widely avaliable in Brazil. Thus, diagnostic cystoscopies should initially be postponed avoiding hospitalization for cystoscopy in the OR. Ultrasound could also be used to evaluate the lower urinary tract during this time of pandemic.

In cases of urological emergencies

In addition to the procedures previously mentioned, non-urologic oncology conditions that deserve urgent treatment are testicular torsion, scrotal abscess and / or Fournier's Syndrome, infection of penile prosthesis or artificial sphincter, priapism and urological trauma. We should consider postponing surgical treatment for all other urological conditions, such as urinary incontinence, prolapses, urethral stenosis, prosthetic implants, infertility-related operations (including vasectomy) and genital procedures such as circumcision or hydrocele correction (15).

Outpatient procedures how should we proceed?

Urodynamic study:

We suggest that urodynamic study programs should be suspended during the crisis period.

Surveillance and follow-up cystoscopy:

Whenever possible, cystoscopies should be postponed. If indispensable, priority should be given to outpatient procedures, using a flexible cystoscope.

It's well known that most programs in developing countries do not have flexible cystoscopy, so it is necessary to perform it in the operating room. This should be postponed whenever possible.

Prostate biopsy

As a rule, prostate biopsies should be postponed, since delaying the diagnosis of prostate cancer for 3-6 months will not interfere with survival outcomes in the vast majority of cases. It's worth discussing prostate biopsy in highly suspicious cases of patients with symptoms related to advanced / metastatic disease, such as bone pain or urinary retention. Given that most medications for metastatic prostate cancer (such as androgen deprivation therapy) are not approved/released without histological confirmation of prostate adenocarcinoma, we recommend to biopsy the most easily accessible site, which may be the prostate (often the most quickly available resource) or some metastasis focus.

However, if clinical signs of metastatic disease are evident, a shared decision should be made with the patient and additional efforts should be performed to expedite the release of these medications even without the biopsy. We believe this exception should be highly considered in selected patients, especially in times of crisis.

If indicated, the biopsy should be performed under local prostatic block, avoiding sedation. As mentioned earlier, additional care must be taken, given the high prevalence of COVID-19 in the stool of infected patients.

Intravesical instillation

- In case of small bladder tumors, consider a single-dose intravesical chemotherapy within 24 hours of TURBT (not immunotherapy). The most commonly used agents are: mitomycin and gemcitabine, in Brazil just gemcitabine isavaiable (16).

- In Intermediate-risk and high-risk non-muscle-invasive bladder cancers: Clinically fit patients with no major comorbidities should receive induction therapy followed by at least 1-year maintenance BCG. In selected cases we can consider postpone one dose during the maintenance. In the case of BCG shortage supply, gemcitabine can be used(16, 17).

How should we manage genitourinary cancers during COVID-19 pandemic?

Patients with D'Amico low-risk prostate cancer

- Treatment: Active Surveillance is recommended for all patients with Grade Group 1.

- Follow-up: Follow-up tests as well as confirmatory and control biopsies should be postponed.

Patients with D'Amico's Intermediate Risk Prostate Cancer

- Treatment: Treatment of these patients should be postponed until the pandemic is over. We have robust evidence to support that postponing treatment in these patients for 3 months do not impact cancer-specific mortality (PROTECT, PIVOT, SPCG 4 trials). Afterward, local treatment should follow the current recommendations in the guidelines (18-20).

- Follow-up: Patients who have already been treated should ideally be followed via telehealth. In-person consultations should only be carried out if they are really necessary. The first post-operative PSA can be performed after 3 months, because no early adjuvant therapy would be initiated in this scenario.

Patients with D'Amico high-risk prostate cancer

- Treatment: We recommend initiation of hormone deprivation therapy immediately and, after 3 months, discuss the most appropriate local therapy. There is good evidence supporting this approach, particularly when associated with radiation therapy and, less common, as neoadjuvant for surgery. While no survival benefit was seen with neoadjuvant studies, pre-operative androgen deprivation therapy reduced positive margin rates as well as extra prostatic extension without compromising cancer control (21).

- Follow-up: Patients who have already been treated should undergo additional tests and visit after the pandemic. In-person consultations should only be carried out if they are really necessary. The first post-operative PSA can be performed after 3 months, because no early adjuvant therapy would be initiated in this scenario.

Biochemical recurrence

No adjuvant radiation therapy may be indicated during COVID-19 pandemic. All cases, even in the presence of unfavorable features, can be managed later with salvage radiation therapy if necessary.

Metastatic prostate cancer

Patients with castration-sensitive disease

We recommend use of ADT in a 6-month formulation (22) in association with Apalutamide 240mg VO daily or Enzalutamide 160mg VO daily (23), when indicated.

If Apalutamide or Enzalutamide is not available, an alternative option is abiraterone 1000mg VO daily associated with prednisone 5mg VO daily. The use of low dose prednisone should be considered since the impact of corticoid usage during the COVID-19 pandemic are not well known (24).

Chemotherapy associated with ADT should be indicated only in extremely selected cases. When indicated, it can be postponed until 120 days after initiation of ADT (25).

Use of colony stimulating factor is recommended in cases of chemotherapy.

Patients with castration-resistant disease

We recommend the use of ADT in semiannual formulation (22) associated with preferably 160mg of enzalutamide VO daily (if not previously received) (26) or alternatively abiraterone 1000mg VO daily associated with prednisone 5mg VO daily (if not previously received).

Alternatively, in patients with isolated bone metastases, the use of radium 223 ADT may be considered (27).

Alternatively, docetaxel with reduced dose every 3 weeks can be considered. It's important to emphasize that colony stimulating factor is highly recommended when chemotherapy is administered (28). Zoledronic acid should be used in patients with bone metastases every 3 months (29).

Localized kidney neoplasm

Asymptomatic cT1a patients should have their treatment postponed, unless there is a rare risk that a nephron-sparing procedure becomes not feasible with the delay of surgery.

Asymptomatic cT1b or cT2 patients, eligible to partial nephrectomy, should be operated to avoid losing the window of a nephron sparing surgery. If the indication is radical nephrectomy, it may be postponed.

Patients with cT3-4 disease and/or with symptoms such as gross hematuria should be operated, especially those with thrombus in the renal vein and / or vena cava.

Metastatic kidney neoplasm

What is the role of cytoreductive nephrectomy in the current scenario? Should we always try systemic treatment first?

We should proceed with cytoreductive nephrectomy whenever this is the best short- and medium-term treatment option for symptoms control. Asymptomatic patients with low and intermediate risk who can wait 3 months to start treatment should wait. Patients with indications of immediate systemic treatment should start treatment despite nephrectomy, especially in cases of intermediate and poor risk (30). Regarding the choice of first line treatment, we favor, if available, the combination of a tyrosine kinase inhibitors (TKI) with immunotherapy, such as Axitinib with pembrolizumab (31, 32).

We also suggest adjusting the dose intervals to less frequent (pembrolizumab to 400mg every 6 weeks). If not available, the choice between the combination of immunotherapy with ipilimumab and nivolumab versus TKI should take into account the risk of complications and potential readmissions (33).

Systemic treatment

It is relatively safe to start systemic therapy with tyrosine kinase inhibitors (TKI) and immunotherapy, although it might have a hypothetical detrimental effect on the immunological response to COVID-19. Nonetheless, no reliable evidence regarding therapy with immunotherapy or tyrosine kinase inhibitors has been identified but the landscape is changing rapidly, and we should be attentive to any evidence that could show the opposite (30).

Non-invasive bladder neoplasm

In general, TURBT should be performed whenever possible. It is important to highlight that we recommend performing a cold-cup biopsy of the base of the lesion to ensure representation of the detrusor muscle and avoid the need for repeat TURBT due to undersampling (16).

Elderly patients with multiple comorbidities and asymptomatic patients with radiologically small and superficial tumors can have the procedure postponed. viRADS staging system may play an important role in selecting such cases.

Repeat TURBT is the standard of care for non-muscle-invasive high-risk bladder tumors (34). However, during the pandemic, some exceptions can be considered. If the initial procedure was performed by an experienced surgeon who is confident that the entire lesion was completely removed and there is presence of muscle layer in the pathology, the repeat TURBT may be postponed. In patients with high-grade pTa, repeat TURBT can also be delayed, even if no muscle is represented.

Invasive muscle bladder neoplasm

Muscle invasive bladder cancer is an aggressive disease with great potential to be curable. In this scenario, surgical delays might represent a loss on the window of treatment.

In general, we recommend performing neoadjuvant chemotherapy and, after finishing, assess the conditions of the hospital to decide on the need for a cystectomy vs bladder preservation protocol (if indicated). Of note, neoadjuvant chemotherapy with cisplatin and gemcitabine before cystectomy can be delayed for up to 6-8 weeks from diagnosis (35).

Cystectomy after neoadjuvant chemotherapy can also be safely delayed for up to 10 weeks post chemotherapy (36) without jeopardizing oncological outcomes (37).

Patients who have undergone cystectomy should consider adjuvant chemotherapy with cisplatin and gemcitabine. This approach still offers survival benefits even 180 days after surgery (38). We should always consider using colony stimulating factor when chemotherapy is recommended.

For patients who wish to preserve the bladder, or who are not eligible for surgery, or the hospital does not have adequate resources, trimodally therapy should be considered. (TURBT followed by hypo-fractionated radiotherapy associated with weekly chemotherapy with gemcitabine 100mg/m^2).

Metastatic bladder neoplasm

For cisplatin eligible patients we recommend first line of treatment (35):

- Cisplatin 35mg/m^2 on days 1 and 8 and gemcitabine 1000mg/m^2 on days 1 and 8 every 3 weeks (39).

- Consider colony stimulating factor in all patients.

First line treatment for patient's cisplatin--inegible

For cisplatin ineligible PD-L1 positive patients we recommend first line of treatment:

- Atezolizumab 1200mg on day 1 every 3 weeks (40) or pembrolizumab 200mg on day 1 every 3 weeks (40).

For cisplatin ineligible PD-L1 negative patients we recommend the first line of treatment:

- Carboplatin, AUC 4.5-5 and gemcitabine 1,000mg/m^2 on day 1 and day 8, every 3 weeks (41).

- Consider colony stimulating factor in all patients.

Testicular cancer (initial diagnosis)

Radical orchiectomy should be performed as soon as possible because it is an outpatient procedure and will guide further treatment. We recommend surveillance for most patients with Stage I over any adjuvant treatment, despite unfavorable features (42).

Stage 2 Testicular cancer

- For low volume stage II patients (IIa and IIb) we recommend radiotherapy instead of chemotherapy for seminomas (42).

- For High volume Stage II seminomas: 4 cycles of EP(Etoposide 100mg/m^2 IV on Days 1-5 and Cisplatin 20mg/m^2 IV on Days 1-5, every 21 days), considering using G-CSF (42);

- For Non-seminoma stage IIA with normal markers: retroperitoneal lymph node dissection might be considered to avoid use of chemotherapy (42).

- For non-seminoma Stage IIA with significant elevation of tumor markers and stage III (for both seminoma and non-seminoma): In case of favorable risk, we recommend 4 cycles of EP. We do not recommend 3 cycles of BEP. In case of intermediate or unfavorable risk, 4 cycles of VIP (Etoposide 75mg/m^2 IV on Days 1-5; Ifosfamide 1200mg/m^2 IV on Days 1-5 with same protection and Cisplatin 20mg/m^2 IV on Days 1-5, every 21 days) are preferable or alternatively, 4 cycles of BEP, (with strong recommendations of G-CSF use), because of the bleomycin pulmonary toxicity (42).

Recommended Reading and updating web sites for healthcare professionals

- Centers for Disease Control and Prevention (CDC). Coronavirus (COVID-19). Available at. <https://www.coronavirus.gov/>

- World Health Organization (WHO). Coronavirus disease (COVID-19) Pandemic. Available at. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>

- Journal of the American Medical Association (JAMA). Coronavirus Disease 2019 (COVID-19). Available at. <https://jamanetwork.com/journals/jama/pages/coronavirus-alert>

- The New England Journal of Medicine (NEJM). Coronavirus (COVID-19). Available at. <https://www.nejm.org/coronavirus>

- The Lancet (Lancet). COVID-19 Resource Centre. Available at. <https://www.thelancet.com/coronavirus>

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Surgical treatment of bulbar urethral strictures: tips and tricks

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ABSTRACT

The surgical treatment of bulbar urethral strictures is still one of the most challenging reconstructive-surgery problems. Bulbar urethral strictures are usually categorized as traumatic and non-traumatic strictures depending on the aetiology. The traumatic strictures are caused by trauma and they determine disruption of the urethra with obliteration of the urethral lumen, ending with fibrotic gaps between the urethral ends. Differently, the non-traumatic urethral strictures are mainly caused by catheterization, instrumentation, and infection, or they can also be idiopathic. They are usually associated with spongiofibrosis of the segment of the urethra that has been involved.

Worldwide, two different surgical approaches are currently adopted for bulbar urethral repair: transecting techniques with end-to-end anastomosis and non-transecting techniques followed by grafting. Traumatic obliterated strictures require transection of the urethra allowing complete removal of the fibrotic tissue that involves the urethral ends. Conversely, non-traumatic, non-obliterated urethral strictures require augmentation of the urethral plate using oral mucosa grafts.

Nowadays, it is still difficult to choose the correct surgical management for non-obliterated bulbar stricture repair. Indeed, different surgical techniques have been proposed (pedicled flap vs free graft, dorsal vs ventral placement of the graft, non-transecting technique using or non-using free graft, etc.) but none emerged as the best solution since all techniques have showed similar success and complication rates. Consequently, the final choice is still based on surgeon's preferences and patient's characteristics.

Within the current manuscript, we like to present some of our tips and tricks that we developed along our prolonged surgical experience on the treatment of bulbar urethral strictures. These might be of interest for surgeons that approach this complex surgery. Moreover, our suggestions want to be useful regardless the type of chosen technique being adaptable for different scenario.

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INTRODUCTION

The treatment of bulbar urethral strictures using end-to-end anastomosis was firstly described in 1914 by Hamilton Russell from Melburne, Australia. Across the years, many authors reported excellent results using excision of urethral strictures and end-to-end anastomosis, with some innovative technical suggestions (1-7). In 2007, we reported our case series of 153 treated patients

that received bulbar end-to-end anastomosis. Between those patients, complications were modest with 14 (23.3%) patients that experienced ejaculatory dysfunction, 11 (18.3%) had decreased glans sensitivity, 7 (11.6%) had the gland neither full or swollen during erection, 1 (1.6%) had a cold gland during erection (8). The scenario of urethral stricture repair was further mutated in 2011, when Andrich and Mundy described a new technique: the non-transecting anastomotic bulbar urethroplasty. Here, the corpus spongiosum and the urethral arteries were not transacted during the procedure. Thanks to the blood supply preservation, the authors described absence of any sort of sexual complications at short and long--term (9). Nowadays, the choice between transecting (end-to-end) and non-transecting (free graft one-stage urethroplasty) techniques is still controversial (10, 11), and yet none of the two techniques has prevailed over the other.

The grafting era of reconstructive bulbar urethral stricture repair started in 1996 when two fundamental techniques were described. Morey and McAninch presented the technique for harvesting the oral mucosal graft from the cheek and the ventral grafting of the urethra (12). Additionally, Barbagli et al. described for the first time the dorsal grafting of the urethra (13) with buccal mucosa. These two different techniques were further described by Barbagli et al. in 2011 and 2012 (14, 15), as well as by many different authors with similar or modified approaches (16-23). Both have largely contributed to improve surgical outcomes in patients treated for bulbar strictures.

The aim of this narrative review is to describe some tips and tricks, as well as useful steps in performing any type of bulbar urethroplasty. Understanding the peri and intra-operative challenges that may lead to better urethroplasty performance with higher satisfaction rate for surgeons and their patients. We included in this review many drawings and intraoperative photos that can be used as examples for the reader to better understand our practice.

MAIN TEXT

Selection of the surgical technique

The appropriate selection of the surgical technique is mainly based on patient's and stricture's characteristics.

Patient features

Age: Older patients are preferred candidates for end-to-end anastomosis instead of graft augmentation. We say that because operating time is shorter, quality of the buccal mucosa graft might not be as good as in young patients, and also because potential adverse sexual events may have a marginal impact on the quality of life of elderly men. In young patients instead, the bulbar urethroplasty should not be a cause of any sexual or ejaculatory dysfunction. In consequence, graft augmentation is usually preferred. Additionally, for the proximal bulbar urethra, the use of the ventral grafting is more safe than the dorsal counterpart. Indeed, during the ventral approach, the urethral dissection is limited to the ventral surface away from vessels and functional nerves. Conversely, aggressive dissection is required using the dorsal approach, with associated higher risk of sexual impairment.

BMI: Obese patients are no ideal candidates for dorsal grafting. Here, the deepest and fatty perineum may render very difficult to access to the dorsal urethral surface, especially for the proximal urethra, increasing the risk of bleeding and subsequent sexual dysfunction.

Previous surgery: In patients with previous hypospadias repair or penile surgery, the retrograde blood supply to the bulbar urethra may be greatly compromised or absent. Thus, the complete transection of the bulbar urethra (and its anterograde blood supply from the bulbar arteries) may cause a bulbar urethral necrosis ending in early stricture recurrence. This should be kept in mind every time we operate these complex patients.

Stricture features

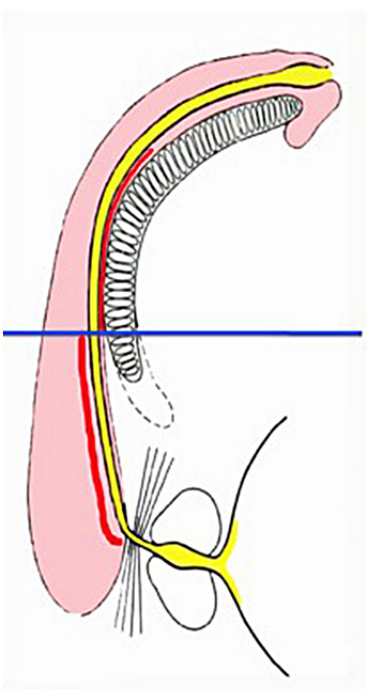
Aetiology: Bulbar strictures related to previous blunt perineal trauma with urethra disruption require end-to-end anastomosis.

Site: In distal peno-bulbar strictures, the end-to-end anastomosis may cause penile cordee and/or sexual dysfunction, and it is consequently not the preferred technique for these types of strictures. Grafting techniques should be instead preferred. However, from the distal bulbar urethra up to the tip of the penis, the spongiosum tissue is thin and does not provide

adequate support for a ventral graft. For these reasons, it is better to use the dorsal onlay approach, and to reserve the ventral approach only for the proximal part of the bulbar urethra, where more abundant spongiosum tissue can supply the graft (Figure-1).

Length: Strictures up to 2 cm are ideal for end-to-end anastomosis. In longer strictures, complete transection of the urethra and subsequent removal of the scarred tissue may create unexpected loss of tissue and longer gap between the two urethral ends. In these situations, end--to-end anastomosis are not recommended since they cannot provide tension-free anastomosis, with consequent higher risk of recurrent stricture. Planning the end-to-end urethroplasty, surgeons need to be mindful that urethrography may underestimate the real stricture length. Moreover, when they perform an end-to-end anastomosis, both the urethral ends should be spatulated for approximately one cm on each side. In consequence, 1 cm stricture requires the removal of 3 cm of urethra shortening considerably the urethra.

Figure 1 - The different location of the graft (in red) according to the thickness of the spongiosum tissue: dorsal location on the distal bulbar urethra, ventral location on the proximal bulbar urethra.



Tips and tricks for bulbar urethroplasty

We like present also some important and useful suggestions to render the surgery safest for the patient and easier for the surgeon.

Preparation of the patient for surgery

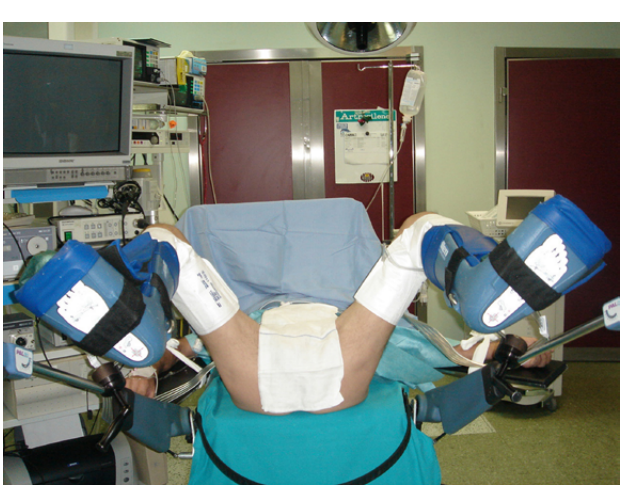
For any bulbar urethroplasty, simple or complex, we suggest to rely on the simple lithotomy position using the Allen stirrups (Figure-2). This might avoid any compression on the popliteal fossa that can cause compartmental syndrome or neuro-muscular problems.

The use of sequential inflatable compression sleeves (Figure-2), greatly reduces the risk of vascular problems to the legs and embolism. Furthermore, the use of these devices is comfortable for the patients during the postoperative recovery because they facilitate the relaxation of the muscles of the lower limbs. For any kind of urethroplasty, we kindly ask to the anaesthesiologist to perform general anaesthesia (no epidural anaesthesia) with controlled hypotension (range 90mmhg - 40mmhg). This suggestion is crucial to avoid bleeding.

Preparation of the urethra for surgeon

Before starting the bulbar urethroplasty we suggest to insert 3Fr guidewire through the urethra (Figures 3A and 3B). The guidewire is an im-

Figure 2 - Simple lithotomy position using Allen stirrups and sequential inflatable compression sleeves.



portant suggestion to avoid any problem during surgery, especially to avoid the risk of losing the proximal urethral lumen. Following the guidewire (Figure-3C), the urethral opening is faster, easier and of course safer.

Harvesting the oral mucosal graft

As suggested by Morey and McAninch in 1996 (12), to harvest the oral mucosal graft, we also rely on a double team. The first one can harvest the buccal mucosa graft, while the second team can carry the urethral dissection and preparation (Figure-4A). The use of the double team reduces the operative time, the risk of cross-contamination during surgery, and it is a good opportunity for young residents to start their training in reconstructive urethral surgery, taking care of the harvesting part of the buccal mucosa graft. In our daily practice, the cheek represents the preferred site for harvesting the graft. A Kilner-Doughty mouth retractor is placed in situ (Figure-4B), and using this retractor only one assistant is required for the harvesting procedure (Figure-4C). For one--stage urethroplasty, we harvest an ovoidal oral mucosal graft (Figure-4D), and we always close the harvesting site (Figure-4E). For 2-stage urethroplasty, we harvest a rectangular graft (Figure--4F), and we don't close the harvesting site (Figure-4G). Using these techniques, we reported a low incidence of early and late post-operative complications or sequelae, but high patient's satisfaction, as reported in a series of 553 patients (24).

The true anatomy of the proximal bulbar urethra

To know well the anatomy of the proximal bulbar urethra is fundamental to whom who want to perform urethral surgery. In the proximal part of the bulbar urethra, the urethral tube does not progress downward inside the spongiosum tissue, but it heads straight to the bladder (Figures 5A and 5B). Thus, when we expose the distal part of the urethral stricture (Figure-5C), it is not necessary to open the spongiosum tissue for the last 3 cm, since the urethra has already turned into the perineum. This approach might also avoid excessive bleeding because it spares the bulbar arteries (Figure-5A). When we approach the urethral lumen, we usually make progressive dilations of the stricture (Figures 6A-C), until 16 Fr. At this point, we check if a nasal speculum can be inserted in the proximal part of the urethra and subsequently we enlarge the proximal lumen by making several incisions of the scarring tissue at 6 o'clock (Figure-6D). We repeat these steps until the speculum can be widely opened (Figure-6E) inside the proximal urethra.

Figure 3 – A) Urethroscopy is performed using 7F instrument; B) The 3F guidewire is inserted through the stricture; C) Following the guidewire, the urethral opening is more faster, easier, and sure.

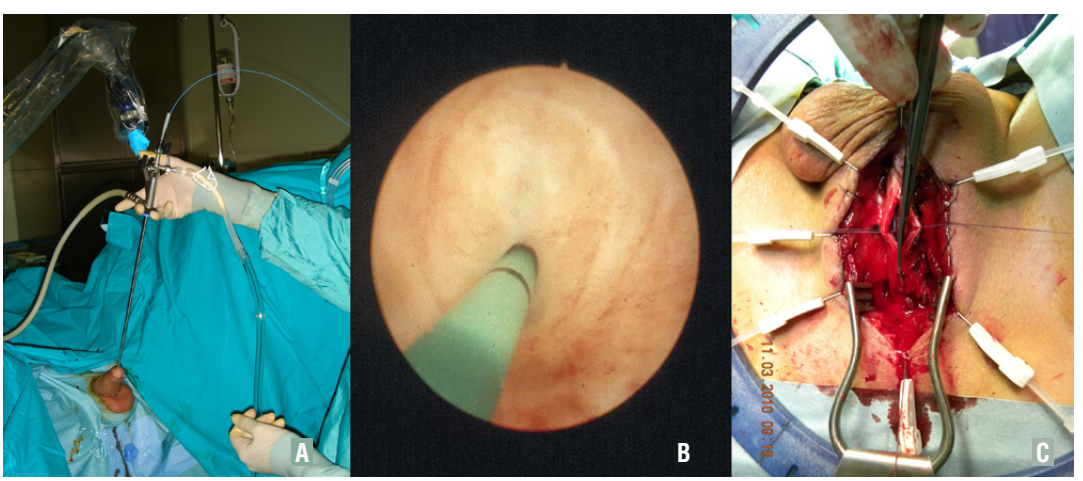


Figure 4 - A) The double team; B) The Kilner-Doughty mouth retractor in place; C) The assistant harvesting the graft; D) Ovoidal shape graft for one-stage urethroplasty; E) Closure of the harvesting site; F) Rectangular shape graft for two stage urethroplasty; G) Non-closure of the harvesting site.

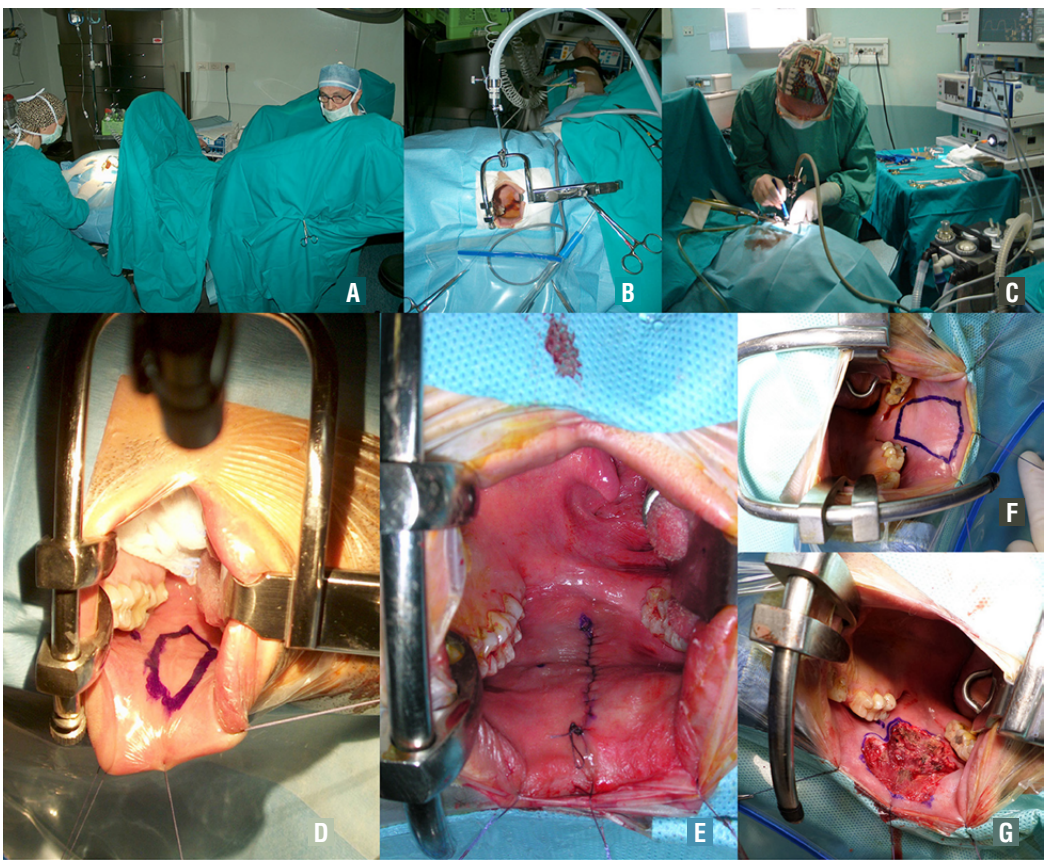


Figure 5 – A) The urethra don't progress downward but heading straight to the bladder; B) The true direction of the proximal bulbar urethra; C) The urethra is ventrally opened and the stricture is evident.

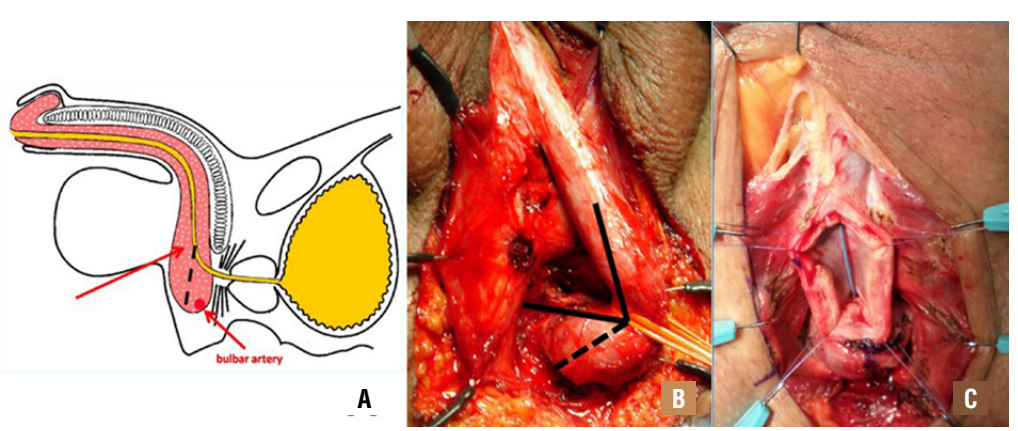
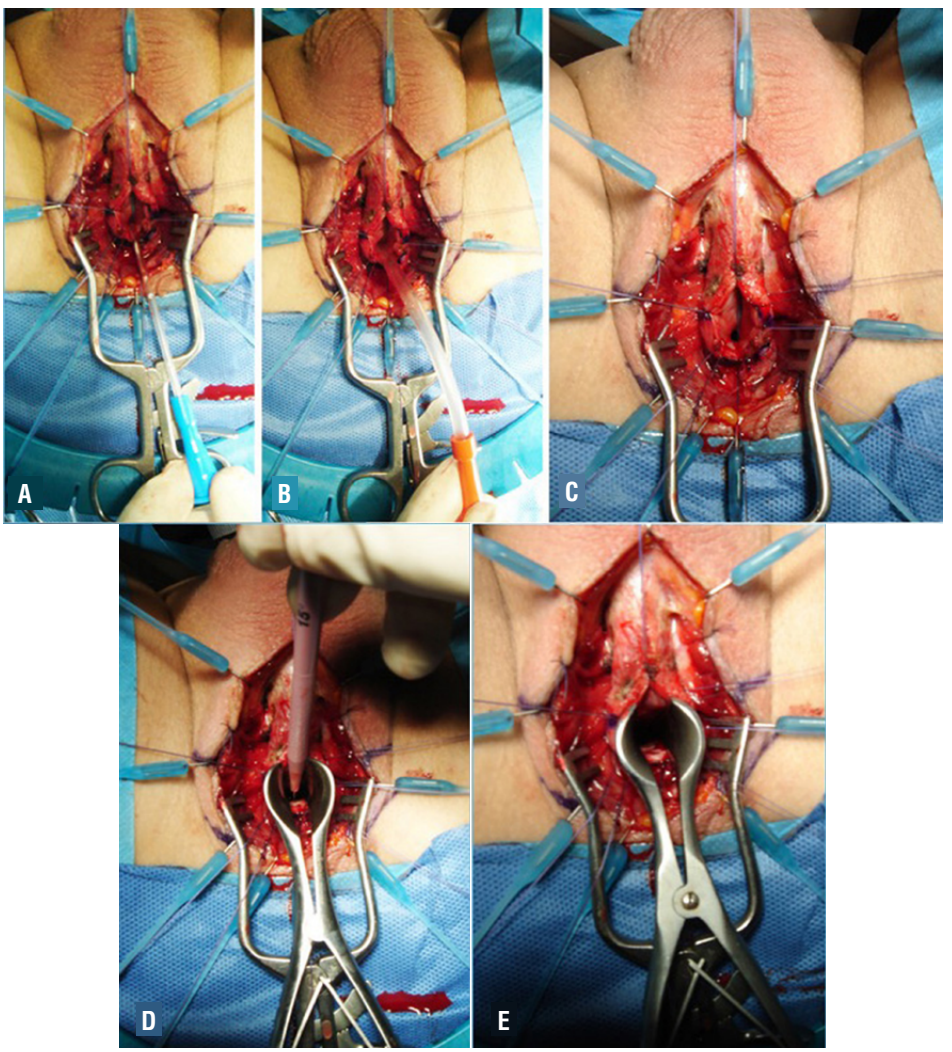


Figure 6 – A-E) Progressive urethral dilation over catheter until 16F.



Anastomosis of the oral graft to proximal urethral mucosa

During ventral onlay graft urethroplasty, it is mandatory to perform the anastomosis between the oral graft and the urethral mucosa as proximal as possible, just in front of the verumontanum. This trick is crucial if we want to avoid recurrence of the stricture on the proximal tract of the anastomosis. Using a 4/0 Vicryl, with the needle modified into a J shape (Figure-7A), we pass the stich, from outside to inside, through the spongiosum tissue until the verumontanum (Figure-7B). Subsequently, the tip of the needle is pushed head toward the bladder (Figure-7C) and withdrew backward outside the urethra (Figures 7D and E). By using this technique, 3 stitches are inserted at 5, 6, 7 o'clock positions near the verumontanum (Figure-7F). The stitches are then passed through the proximal end of the oral graft (Figure-8A), and when they are tied up, the oral graft is moved towards the verumontanum (Figure-8B), filling the gap.

CONCLUSIONS

Within the current review we reported many tips and tricks that we developed, over the past years, and that we have progressively integrated in our daily practice. These suggestions have

Figure 7 – A) The j-shape needle; B) The needle is moved in front up to the verumontanu; C) The needle is pushed head into the bladder; D and E) The needle is withdrawing back; F) Three stitches are inserted at 5, 6, 7 o'clock near the veru montanu.

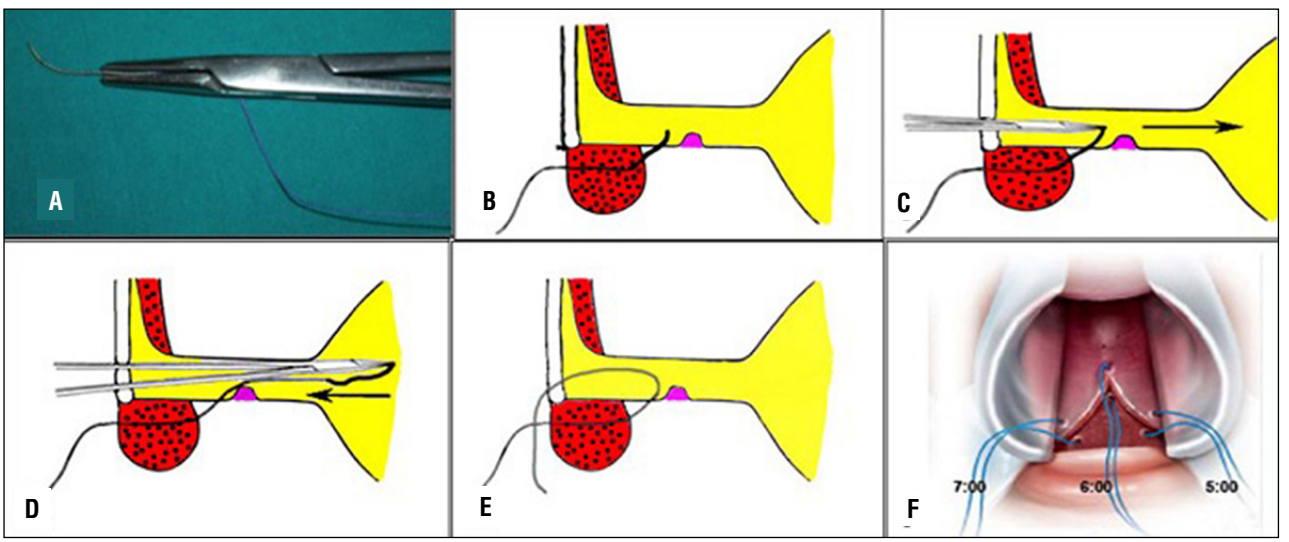
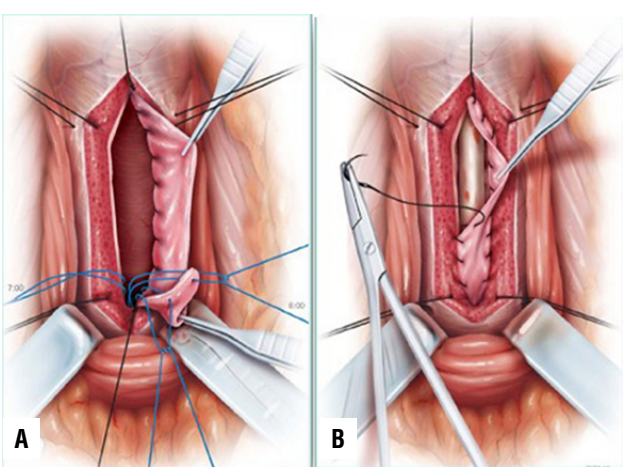


Figure 8 – A) The 3 stitches are inserted into the proximal end of the graft; B) The graft is moved near the veru montanu.



been used for any type of bulbar urethroplasty, resulting in shorter surgical time and lower incidence of post-operative complications. Taken together, the experience that we have maturated over these years has increased the safety and the success rate of our urethroplasties. Noteworthy, the choice of the surgical technique is still a surgeon choice, rather than a "guideline recommended" approach. Surgeons should always take into account patient's (age, BMI, previous surgery) characteristics and stricture's (aetiology, site, length) features before choosing the appropriate technique. The available literature provides many reports about different techniques, but we believe that the surgical experience, as well as surgical preference and background still represent the most important factors that should influence the choice of the correct approach. We hope that our suggestions might help surgeons to improve their daily surgical practice.

CONFLICT OF INTEREST

None declared.

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Buried penis repair: tips and tricks

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ABSTRACT

Obesity is increasing in prevalence worldwide and an increasingly commonly encountered condition is adult acquired buried penis (AABP). We review the current management of AABP and relevant literature. Management of AABP requires a combination of genitourinary reconstructive techniques and plastic surgery techniques that are unique to this condition. We offer our experience and tips and tricks for the treatment of AABP.

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INTRODUCTION

Obesity is increasing in prevalence worldwide, with rates nearly tripling from 1975-2016 (1). This is associated with numerous comorbidities, including type 2 diabetes mellitus, obstructive sleep apnea, coronary artery disease, stroke, and various cancers, to name a few (2). Unfortunately, the genitourinary system is not spared, as obesity is also associated with adult acquired buried penis (3). Adult acquired buried penis is not a benign condition; it causes significant psychosocial distress. In addition, a recent study suggested that it was associated with a higher incidence of penile carcinoma (4). Adult acquired buried penis is also associated with concomitant urethral strictures, with rates as high as 31-47% (5, 6), likely due to associated lichen sclerosis and chronic inflammation. These can complicate repair and often demand their own attention either prior to or coincident with buried penis repair.

While obesity is not the sole etiology of adult acquired buried penis, as it can also result from cicatrix formation due to overzealous

circumcision, penile skin loss resulting from lichen sclerosis, or, rarely, pelvic lymphedema, it remains one of the most significant risk factors for the development of this condition. Unfortunately, weight loss alone is often ineffective and definitive treatment requires surgical repair.

Operative techniques have been previously documented in the literature (7-10), but typically include the following general steps: dorsal slit to expose the glans followed by degloving of the diseased penile skin, escutcheonectomy with or without panniculectomy, and harvest and application of split thickness skin graft Jun et al. (9) described their operative technique in a previously published article. Some notable items from their technique include using the anterior thigh for their split thickness skin graft (as opposed to using the resected skin from the panniculectomy/escutcheonectomy (8, 10) or other harvest sites) and securing their grafts with fibrin sealant after suturing proximally and distally Pariser at al. (5) recently proposed a classification system to stratify buried penis repair by complexity of repair. This includes the following categories: Category I – penile unburying with local skin flap; Category II – use of skin graft; Category III – scrotal surgery; Category IV – escutcheonectomy; and Category V – abdominal panniculectomy. When reviewing outcomes based on classification, more complex repairs (i.e. Category III-V) were associated with higher incidence of high-grade complications including wound dehiscence, abscess requiring operative intervention, and scrotal hematoma, among other complications.

In this article, we review the current literature on adult acquired buried penis repair as well as offer several tips and tricks we use in our practice.

DISCUSSION

Pre-operative Evaluation

Our pre-operative evaluation generally consists of a comprehensive medical and surgical history as well as a physical examination. Given the aforementioned co-morbidities often associated with adult acquired buried penis, it is imperative that patients' other medical issues are optimized prior to any surgical intervention. Additional evaluations include assessing baseline erectile function and voiding symptoms. In our practice, all patients are administered the American Urologic Association Symptom Index. Because of the high rates of comorbid urethral stricture disease (5, 6, 11), if patients are found to have symptoms suggestive of a stricture, further evaluation is performed. This can include either a pre-operative retrograde urethrogram or intra-operative urethroscopy. Often a perineal approach such as a Kulkarni urethroplasty is required for longer segment or proximal strictures, and these are usually performed prior to a buried penis repair with at least six months between the two procedures to allow appropriate healing. More distal strictures can be managed at the time of buried penis repair.

Tip #1: We recommend screening all AABP patients for potential urethral stricture using validated voiding symptom questionnaires such as the AUA-SI and performing either urethroscopy or retrograde urethrogram as indicated;

Tip #2: Should a patient require a urethroplasty prior to buried penis repair, we recommend allowing at least 6 months between surgeries.

Management of Cicatrix, Escutcheonectomy and/or Panniculectomy

Although most commonly the penile skin is diseased or obliterated due to lichen sclerosis or chronic inflammation, there are rare instances in which the penile skin is salvageable. These typically result from overaggressive circumcision. In these cases, one described technique for unburying is a ventral slit with scrotal flap (12). In this technique, a ventral slit is made to expose the glans, the incision is carried down the median scrotum from midshaft to the mid scrotum, and a relaxing incision is carried from the mid scrotum horizontally to create a rotational flap. The ventral penile skin defect is then covered using the scrotal skin before closing the scrotum. With this technique, the dorsal penile skin is viable and maintained.

However, the majority of cases of adult acquired buried penis are the result of morbid obesity and chronic inflammation, and in many of these cases the penile skin is nonviable. In these cases, the penile skin is completely degloved, taking extreme care to avoid leaving a remnant of skin near the corona, as any remnant can become

an edematous ring of tissue. The escutcheon is resected to the level of the abdominal wall fascia. If there is any lymphedematous tissue, the entirety of the diseased skin, underlying dermis, and Dartos tissue should be resected to ensure removal of the lymphatics and prevent reburying. One additional important step is to secure the remaining suprapubic flap to the pubic bone or Buck's fascia in order to prevent disease recurrence. We often place drains to promote healing, although not all surgeons do the same (13).

Tip #3: Ensure that the entirety of the penile skin is removed, particularly near the corona to avoid leaving an edematous ring of diseased tissue;

Tip #4: To avoid recurrence of adult acquired buried penis due to lymphedema, it is imperative that the entirety of the diseased skin, dermis, and dartos tissue is resected to remove the lymphatics;

Tip #5: When performing escutcheonectomy, ensure that the skin is secured to Buck's fascia or the pubis to prevent re-burying.

Harvest and application of split thickness skin graft

Typically, we prefer to harvest our skin graft from the lateral thigh. However, others have reported successful outcomes when using sections of the resected escutecheon or pannus (8, 10), though care should be taken to ensure that the used segments are free of any lymphedema or signs of chronic inflammation.

When applying the graft, the penis is held on stretch, usually with the assistance of retention sutures placed through the glans at the start of the procedure. To prevent a cleft from forming at the base of the penis, it is helpful to advance a collar of scrotal skin and escutcheon skin around the base of the penis and secure the proximal end of the graft to this collar. Holding the penis on stretch while securing the graft proximally to Buck's fascia and distally to the corona ensures that the graft will not fold on itself and will be appropriately apposed to the underlying tissue Iblher et al. (14) reported success with adjuncts such as intracavernosal prostaglandin injections or daily tadalafil post-operatively to promote penile engorgement and prevent graft contracture.

Tip #6: Apply the split thickness skin graft to the penis while on full stretch;

Tip #7: To prevent a cleft from forming at the base of the penis, advance a collar of scrotal and/or escutcheon skin around the penile shaft at the base and secure the split thickness skin graft to this collar.

While not typically used in our repairs, wound vacuums offer several benefits for healing and graft take. These include promoting microcirculatory flow and stimulation of angiogenesis, preventing graft lift by constant evacuation of fluid, exudate, and blood, and preventing graft shear (15).

Post-operative care

At our institution, patients are typically admitted for 48 hours with foley catheter removal on post-operative day 2. Dressings are typically taken down on post-operative day 2 and drains are removed within the first 5-7 days. However, a recent case series published by Erpelding et al. (13) demonstrated the feasibility of same day discharge for patients undergoing buried penis repair. In their series, 10/16 patients were discharged same day with no differences in complication rate compared with those patients kept overnight. These patients were typically discharged with a foley catheter and a penile bolster dressing, both of which were then removed at a post-operative visit one week later. Interestingly, complexity of repair did not influence whether patients were kept overnight.

Despite the invasiveness of a buried penis repair, most patients, when asked, would have the surgery performed again due to their significant improvements in sexual function, voiding function, and overall quality of life (8, 16, 17). Theisen et al. (16) reported significant patient-reported in sexual domain and urinary domain, with 87.5% reporting improvement in overall urinary bother and 94% reporting improvement in their overall ability to function sexually. Similarly, a retrospective review by Hampson et al. (8) showed improvements in erectile function, sexual activity, genital hygiene, and ability to stand while urinating, among other improved functional outcomes. Importantly, these improvements were sustained at a mean of 39.4 months of follow-up. In addition, 85% of patients

in their series stated that they would undergo the procedure again. Rybak et al. (17) quoted a 91% improvement in voiding erectile dysfunction, and quality of life, respectively, in patients undergoing buried penis repair. Thus, a properly performed buried penis repair achieves sustainable, satisfactory results and can have a significant impact on a patient's overall well-being.

CONCLUSIONS

As the incidence of obesity increases, so to will our encounters with patients who have developed adult acquired buried penis. Definitive treatment typically requires surgical repair to unbury the phallus and can lead to significant improvement in a patient's quality of life. It is imperative that the reconstructive urologist be comfortable with surgical techniques involved in buried penis repair. We offer several of our own tips and tricks to assist in achieving successful patient outcomes

CONFLICT OF INTEREST

None declared.

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Brazilian consensus on vesicoureteral reflux–recommendations for clinical practice

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ABSTRACT

Introduction: Vesicoureteral Reflux (VUR) is characterized by a retrograde flow of urine from the bladder into the ureters and kidneys. It is one of the most common urinary tract anomalies and the major cause of urinary tract infection (UTI) in the first years of life. If not properly diagnosed and treated can lead to recurrent UTI, renal scar and, in severe cases, to end stage renal disease. Despite recent advances in scientific and technological knowledge, evaluation and treatment of VUR is still controversial and there is still considerable heterogeneity in evaluation methods and therapeutic approaches. The aim of the present consensus is to give a practical orientation on how to evaluate and treat VUR.

Methods: The board of Pediatric Urology of the Brazilian Society of Urology joined a group of experts and reviewed all important issues on Vesicoureteral Reflux evaluation and treatment and elaborated a draft of the document. On November 2017 the panel met to review, discuss and write a consensus document.

Results and Discussion: Vesicoureteral Reflux is a common and challenging problem in children. Children presenting with Vesicoureteral Reflux require careful evaluation and treatment to avoid future urinary tract infections and kidney scars. The panel addressed recommendations on up to date choice of diagnosis evaluation and therapies.

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INTRODUCTION

Vesicoureteral reflux (VUR) is defined as the backflow of urine into the ureter and kidney. It is one of the most common urological anomalies in children with an incidence of 0.5% to 3% in the general pediatric population (1, 2). This incidence increases to 30 to 40% in children with history of

urinary tract infection (UTI) (3, 4). The incidence of VUR in siblings of a child that has VUR varies from 26 to 46% (5).

The backflow of urine into the kidney predisposes bacteria to ascend causing pyelonephritis. The immunologic and inflammatory response to the infection may lead to renal lesions and formation of renal scars (6, 7).

VUR is one of the most important diseases of childhood and, when not properly treated, presents high morbidity and can lead to significant renal damage and, if severe, consequent hypertension and chronic renal failure. Reflux nephropathy is responsible for up to 25% of cases of end stage renal disease (8).

The two most common forms of VUR presentation are urinary tract infection (UTI) and prenatal hydronephrosis. With the advent of antenatal ultrasound (US) more reflux cases are being diagnosed on the neonatal period. Of all cases of prenatal hydronephrosis, 15 to 21% are caused by VUR (9, 10). Older children will mostly often be diagnosed after a febrile UTI.

VUR is classified according the degree of ureteral, renal pelvis and calix dilation and varies according to severity from grade I to V (Figure-1) (11). The use of a classification system is important to guide therapeutic approach, since lower grade VUR has a greater chance of spontaneous resolution and will benefit from more conservative treatments (12).

Investigation and management of VUR management is still controversial. Voiding Cystourethrography (VCUG) is considered the gold standard for diagnosing and evaluating VUR grade. Catheterization for VCUG can be traumatic for both the child and family (13). Not all children with UTI will present VUR, and of those with VUR, not all of them will present renal scar. Therefore, the indication of a VCUG for all children with prenatal hydronephrosis or UTI is debatable (14-17). Another important tool in the evaluation of VUR is the scintigraphy with DMSA (dimercaptosuccinic acid). DMSA scan is mostly used to investigate the impact of VUR in the kidney by analyzing function and the presence or not of renal scars. Debate whether it should be used in the acute phase of an UTI to rule out pyelonephritis and allow to avoid VCUG or in a later phase (4 to 6 months after UTI) to evaluate for scar formation is still debatable (18).

In the same way, the role of antibiotic prophylaxis and surgical treatment (endoscopic or ureteral reimplantation) have also been questioned and there is no clear indication of which the best treatment modality would be, especially in VUR of low or intermediate grades.

This Brazilian Guideline on evaluation and treatment of VUR has no intention to answer all these questions but to guide urologists, pediatricians, and pediatric nephrologists on the most recent aspects related to the management of children with vesicoureteral reflux.

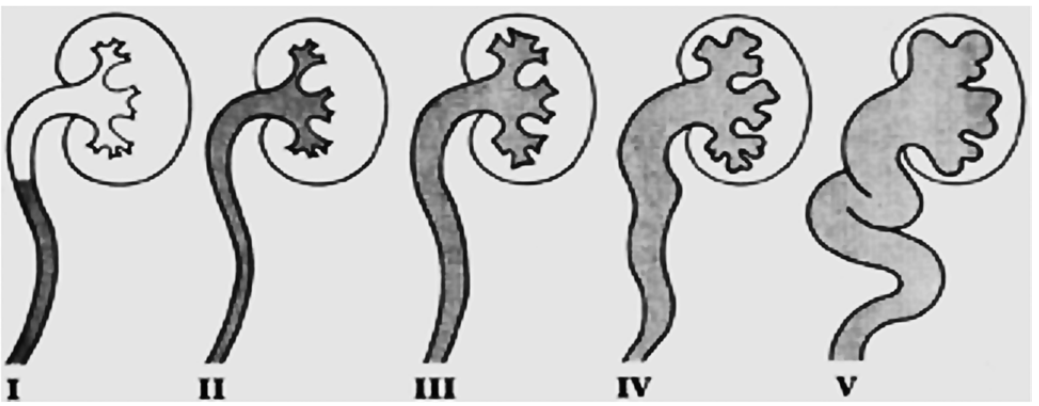
MATERIALS AND METHODS

The board of Pediatric Urology of the Brazilian Society of Urology, noticing the need of a Brazilian guideline on vesicoureteral reflux, joined a group of experts to review the important issues on VUR and elaborated a consensus document. Eight renewed pediatric urologist with known experience in dealing with urinary tract infections and vesicoureteral reflux were invited to participate in the elaboration of a document with the scope of the guiding urologists, pediatricians, nephrologists and others that deal with children with vesicoureteral reflux on the most important and up to date aspects of the evaluation and treatment of those children.

All panel members were instructed to perform a literature search on MEDLINE, EMBASE and COCHRANE LIBRARY databases as well as a review of the base of practical guidelines database for the last 20 years using the term “vesicoureteral reflux”. Papers were selected according to their level of evidence, giving more importance to meta-analysis, systematic reviews, and randomized controlled trials. Cohort and series of patients were used to add information. Review papers and guidelines were used as orientation for which topics and aspects would be included.

After the papers were selected, each member of the group was designated one topic to review and write an orientation document based on the recommended literature.

Figure 1 - International Classification of VUR.

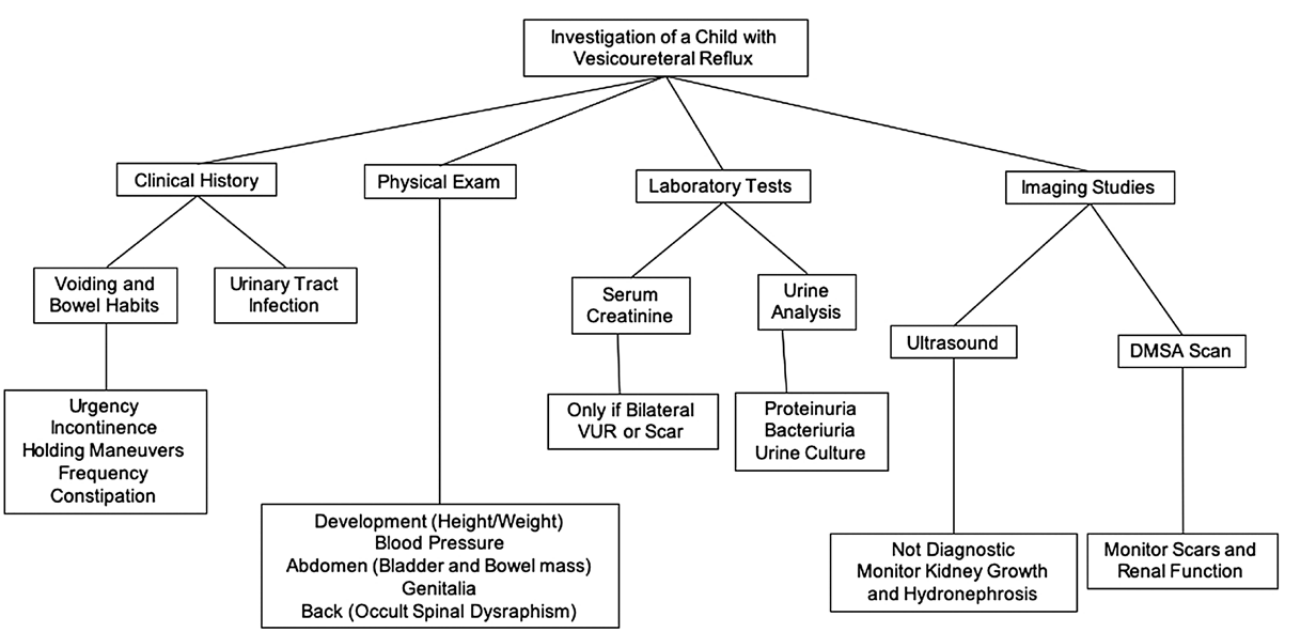


On November 2017, all members joined together during 2 days to review and discuss the previous written documents of each topic and prepare the consensus document. Further discussions, corrections, and revisions were carried out digitally, until all members of the panel have approved this final document. A paragraph containing the panels opinion ("consensus") was added at the end of each section to guide the reader about the information provided and the most common practice on each specific subject.

CLINICAL EVALUATION AND DIAGNOSIS (Figure-2)

As in all fields of medicine, a careful clinical history is very important for the diagnosis. Aspects related to the presence of prenatal hydronephrosis, past episodes of febrile and non-febrile UTI should be investigated. Understanding voiding and bowel habits are important since lower urinary tract dysfunction (LUTD) and constipation are often associated with UTI and VUR (19-21). VUR

Figure 2 - Clinical investigation of a child presenting VUR.



diagnosed in the neonatal period is more common in boys and of a higher grade (22) and is related to high bladder pressure and post-voided residual urine (23). High bladder pressure in infancy may predispose or difficult spontaneous VUR resolution (21, 23).

In all toilet trained children, a very meticulous clinical history of their voiding symptoms, such as increased voiding frequency, incontinence, urinary urgency, holding maneuvers, and also, constipation should be taken. Physical examination should include assessment of weight, height, and blood pressure, palpation of the abdomen looking for masses and globus vesicalis, presence of feces in the bowel, and evaluation of the genitalia. Examination of the back in search for skin markers suggesting occult spinal dysraphism is important since VUR is present in up to 25% of children with spinal dysraphism (24).

Clinical history should be periodically reevaluated during follow-up, since symptoms may change. LUTD and constipation should also be frequently assessed during the course of treatment.

The final diagnosis of VUR will be obtained only with an imaging test. The imaging test for defining VUR diagnosis should be ideally radiation free, with no need for urethral catheterization or sedation, presenting high accuracy and anatomical detailing and with low cost. Unfortunately, none of the currently available imaging tests (VCUG or direct cystocinthigraphy) fills all or most parameters named before.

Laboratory Tests

Serum creatinine dosage is indicated in cases of bilateral high grade VUR and/or presence of bilateral renal scars, being a parameter to estimate the rate of glomerular filtration and as a baseline for future comparisons.

Urine analysis, including proteinuria, bacteriuria, and urine culture are recommended for the diagnosis of VUR and subsequently for suspected UTI. The recommended method for urine collection in children that are not yet toilet-trained is via clean urethral catheterization to avoid contamination (25, 26).

We do not recommend periodic urine analysis and urine culture in asymptomatic children. Investigation of UTI in cases of fever of undetermined origin in patients with VUR must always be performed.

IMAGING STUDIES

Ultrasound

Ultrasound is not accurate in predicting the presence of VUR and should not be used for the diagnosis of VUR (27-29).

Ultrasonography of the urinary tract is recommended to monitor renal development, as well as assess the occurrence or worsening of hydronephrosis, and presence of post voided residue urine. It is important to observe bladder filling during the exam, as this may be correlated with the degree of renal dilation. Ultrasound examinations should be performed at least every 6 months.

Renal Scan

The goals of DMSA scan are to look for the appearance or progression of renal scars and monitoring renal function (30, 31). The best time to order a DMSA scan for the evaluation of VUR is still debatable. Two different approaches have been proposed with the DMSA scan done either in the acute phase of an UTI episode or after 6 months post-infection (25, 32, 33).

The “top-down” approach, which means that the evaluation starts from the kidney by ordering the DMSA scan during the acute phase of the UTI was proposed with the aim to avoid unnecessary VCUG and has a sensitivity of up to 95% (34). In this approach VCUG is only ordered in those with an abnormal DMSA scan. A problem regarding this “top-down approach” is that a second DMSA scan may be needed after 6 months of the UTI to evaluate scar formation.

On the contrary, the “bottom-down” approach (25) advices that the DMSA scan should only be performed 6 months after the UTI with the main goal to evaluate the presence of permanent scars.

In a less invasive way of evaluating children with UTI DMSA, scan would be ordered only in cases of febrile UTI, high grade VUR (IV and V), and changes on ultrasound suggestive of renal lesions.

As for periodicity, DMSA scans should be repeated only after presentation of new episodes of febrile UTI.

Voiding Cystourethrography (VCUG)

Voiding Cystourethrography (VCUG) uses iodine as a contrast medium and allows the classification of VUR as well as evaluation of bladder and urethral anatomy. Because reflux may be an intermittent phenomenon, the test should be performed with fluoroscopic monitoring and with more than one bladder filling cycle, not to exceed three cycles.

It is recommended that it should be done at earliest convenience following UTI treatment (35), confirmation of a sterile urine and with antibiotic coverage due to the risk of onset of a new episode of UTI (36).

The main advantage of VCUG over Direct Isotopic Radionuclide Cystography is related to the anatomical detail. In addition, the current VUR grading system is based on VCUG. Therefore, VCUG remains the gold standard diagnostic test and initial evaluation of VUR.

Direct Isotopic Radionuclide Cystography (DIRC)

Direct Isotope Radionuclide Cystography can replace VCUG for the diagnosis or follow-up of patients with VUR. In this method, a radio-isotopic tracer (usually diethyltriaminepentaacetic acid-DTPA) is infused in the bladder after urethral catheterization and images are obtained during bladder filling and emptying.

Although radio-isotopic method is believed to have less radiation exposure (3), a recent study demonstrated higher radiation exposure compared to fluoroscopic cystography (37). A good correlation was seen between DIRC and VCUG in diagnosing VUR (38) although DIRC has the disadvantage of low definition of image, not allowing the anatomical evaluation of the bladder and urethra, nor proper VUR classification (3). The use of DIRC is preferred during clinical follow-up or evaluation of surgical treatment result.

Other exams in the diagnosis of VUR

Other methods have been developed in an attempt to reduce the morbidity of traditional exams (VCUG and DIRC) in the diagnosis of VUR. Ultrasonographic Cystography has been shown to be very accurate in diagnosing VUR (39, 40) although its use is not yet widespread. Indirect Magnetic Resonance Cystography although is an option to avoid radiation and catheterization, it has been shown to be less sensitive than VCUG in diagnosing lower grade VUR and with higher cost (41, 13).

Consensus

The panel believes that a careful and meticulous clinical history considering all aspects discussed above and with special attention to LUTD should be obtained prior to any imaging test. All children should be evaluated with a renal ultrasound with the evaluation of post-voided residual urine. Renal Scans with DMSA should be reserved for those with history of febrile UTI, VUR grade IV or V and ultrasound suggesting renal lesions. VCUG should be the imaging test of choice for the diagnosis of VUR. DIRC should only be indicated on the follow-up, especially after surgical treatment.

WHO WILL BENEFIT FROM INVESTIGATION

The indication for VCUG may vary according to the clinical presentation of the patient and some protocols have been proposed for this purpose.

Children with urinary tract infection

The indication of a VCUG in the evaluation of a child presenting UTI is still controversial. Children presenting febrile recurrent ITU and/or in cases where alterations of the urinary tract are found in the ultrasonography should be evaluated with a VCUG (25).

Despite that requesting a VCUG after the first episode of febrile UTI in infants is still questioned by some authors, we believe that it could be done in those cases (1).

On the other hand, in older children with recurrent afebrile UTI, VCUG is exceptionally indicated, since the main etiology of UTI in this group of patient is LUTD (42).

Children with Antenatal Hydronephrosis

VCUG is recommended in newborns with postnatal ultrasound findings of bilateral grade II to IV and unilateral grade III to IV hydronephrosis-Society of Fetal Urology-SFU (43, 44), signs of duplicity with hydronephrosis, ureterocele, ureteral dilatation and vesical changes.

For grade II hydronephrosis its indication is controversial, but there may be benefits. In case of degree I hydronephrosis its routine indication may be dispensable.

Siblings and Children of Patients with History of VUR

Routine investigation of asymptomatic siblings and/or children of patients with VUR is controversial. The lack of randomized clinical trials to detect VUR in these patients makes it difficult to routinely recommend it. Parents of children with VUR must be informed that there is a high prevalence of reflux in siblings and offspring, and if the decision is made to investigate, the initial examination should be ultrasonography, with VCUG reserved only for cases of significant changes on ultrasound or after UTI episodes (45, 46).

Consensus

Although the indications for investigation of VUR in children presenting UTI are controversial, the panel agrees that is mandatory that all children with febrile UTI and changes in the ultrasound, and infants with UTI, regardless of changes in US, must be investigated, and encourages investigation of children with well documented UTI, regardless of changes in US. Older children should be carefully evaluated for LUTD. Children presenting with prenatal hydronephrosis should only be routinely investigated if they present high-grade hydronephrosis (grades III and IV) or if ureteral dilation. Investigation of siblings and offspring of patients with VUR should be discussed with the family and, if investigation is the option, it should start with US.

CONTINUOUS ANTIBIOTICS PROPHYLAXIS (CAP)

The use of low-dose antibiotics to prevent UTI in children with VUR is based on the observation that VUR has a high spontaneous resolution rate in the first 4 to 5 years of life (80% grade III VUR, 30-50% grades III-IV) (47-50) and has been indicated for more than 4 decades. This clinical practice is based mainly on expert opinions and, until recently, with few randomized and controlled trials (51-53). Since the 2000s, better quality studies have begun to question whether CAP actually protects children with VUR from pyelonephritis and the formation of new renal scars and if there is a specific group of children who would benefit most from this practice (54-57).

Recently, a large multicenter, randomized study including 607 children with VUR diagnosed after the first or second UTI and with a 2-year clinical follow-up demonstrated that CAP is associated with a significant reduction in the risk of UTI episodes but not new scars (Grade of Recommendation A) (58). Recent meta-analysis have demonstrated benefits of CAP in infants with all degrees of VUR (59-62).

The duration of CAP is still controversial. One option would be to perform VCUG periodically (intervals of not less than 1 year) and, if there is resolution of the reflux, stop the CAP. Another option is stop CAP in toilet trained children with no LUTD. In children who, even when using CAP, present new episodes of UTI, surgical treatment should be an option (2).

Types of Medications Used in Reflux Antibiotics Prophylaxis

Continuous antibiotic prophylaxis, when instituted, should be adequate for the child's age group and the antimicrobial susceptibility pattern of the population in the area the child lives.

The drug of choice should be well tolerated, with low risks and side effects and be affordable, considering ongoing treatment. The dose to be administered is between 25 to 50% of the therapeutic dose, which should be adjusted periodically, according to the child's weight gain, which is more significant in the first year of life. The drug of choice in infants, in the first 6 months of life, by the availability and drug safety, should be Cephalexin or Amoxicillin. Use of Sulfamethoxazole and Nitrofurantoin are not indicated before 2 months of age. For children older than 6 months of age, the options would be Cephalexin, Amoxicillin, Sulfa-

methoxazole/Trimethoprim, Nitrofurantoin or Nalidixic Acid.

Consensus

Based on the studies discussed above, the recommendation of this panel is that CAP should be indicated in all infants and children who have not yet completed sphincter training and who present VUR grade III or higher. However, those with VUR grade I and II also appear to benefit from CAP and the decision should be made after discussing with the family.

FACTORS RELATED TO SPONTANEOUS RESOLUTION OF VUR (Figure-3)

The management of VUR aims to prevent the onset of new episodes of UTI and loss of renal function. Clinical treatment consists of continuous administration of low-dose antibiotics to maintain sterile urine and thereby prevent pyelonephritis and formation of renal scars. The basis of clinical treatment is the expectation of spontaneous resolution, since VUR tends to decrease in grade or completely resolve with time (48, 50). The identification of factors that predict spontaneous VUR resolution may contribute to family counseling at the time of diagnosis and assist in the choice of treatment strategies.

Main factors that predicts spontaneous resolution are

Grade of VUR: The higher the grade of the VUR, the lower the chances of spontaneous resolution. Refluxes of dilated degrees (IV and V) present a probability of spontaneous resolution of 5 to 20%, while in VUR grades I and II resolution occurs in more than 80% (48, 50, 63, 64).

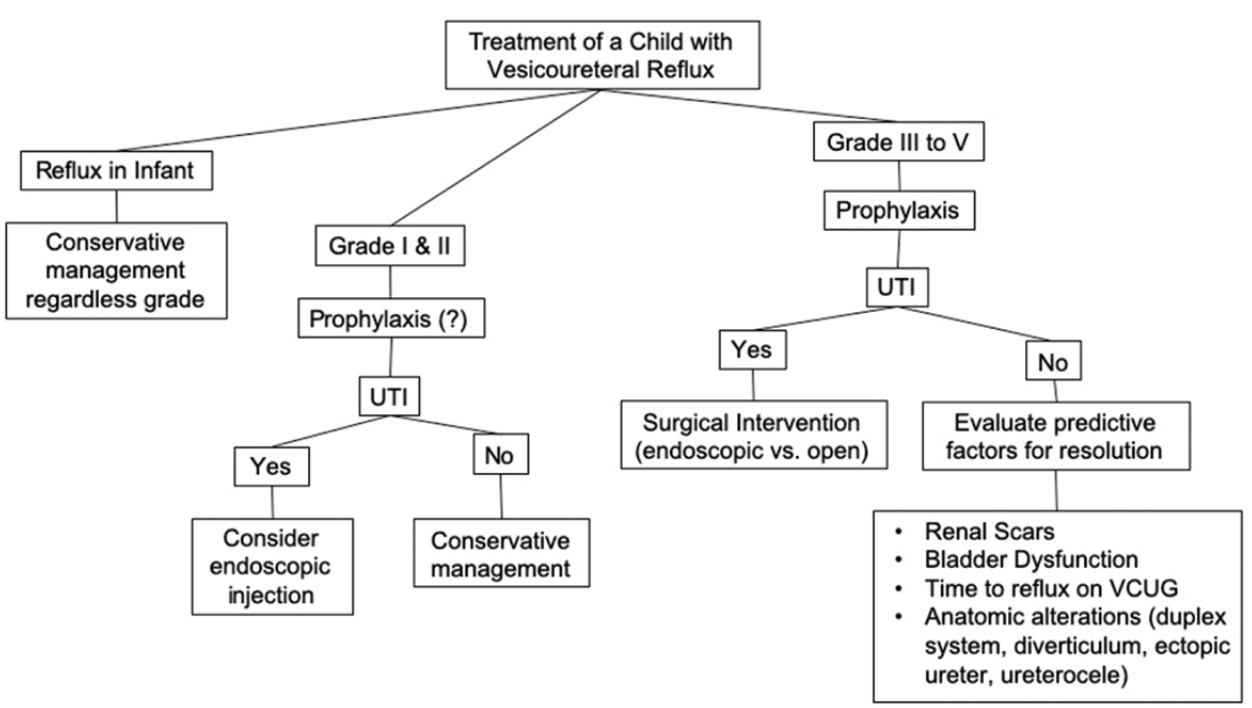
Age at Presentation: VUR presenting in postnatal evaluation or before 1 year of age are associated with earlier resolution (50 ,65, 66).

Gender: Boys with VUR tend to present spontaneous resolution prior to girls (67).

Laterality: Bilateral high-grade VUR (III to V) presents a lower probability of spontaneous resolution compared to unilateral VUR (50, 67).

Abnormalities on DMSA: When renal scars or functional deficit are present there will be

Figure 3 - Management of VUR.



lower chances of spontaneous resolution of VUR (1, 68, 69).

Infused Volume at Presentation of VUR on VCUG: Refluxes that appear in the early stages of bladder filling present smaller possibilities of spontaneous resolution, whereas refluxes that appear only during urination present higher resolution rates (63, 64, 70).

Urinary Tract Infection: The development of an UTI episode during clinical follow-up is a negative predictor for VUR resolution (71) and a sign that clinical approach should be reviewed and an alternative intervention may be required (44).

Bowel and Bladder Dysfunction: The presence of LUTD and/or constipation has a negative impact on VUR resolution.

Diameter of the Distal Ureter: The diameter of the distal ureter is an independent predictor of spontaneous resolution of VUR. As smaller is the diameter of the distal ureter, the greater the chance of spontaneous resolution (47).

Associated Anomalies: The presence of pyelo-ureteral duplicity or para-ureteral diverticulum are some of the anatomical factors related to reduction of spontaneous resolution (50, 64, 70).

Consensus

The panels opinion is that all the above mentioned factors should be evaluated and taken into consideration when discussing with the family the therapeutic options for treating a child with VUR. This panel strongly recommends that treatment of LUTD and constipation should precede any intervention for treatment of VUR (1, 68, 72). The use of nomograms and calculators may be helpful in the evaluation of the chances of a new breakthrough UTI (73) and of spontaneous resolution of the VUR (64, 70).

SURGICAL RECOMMENDATIONS FOR THE TREATMENT OF VUR (Figure-3)

There is a lack of prospective studies with a control group to establish a safe guideline for VUR treatment. Thus, it is not possible to produce recommendations with a high level of evidence.

The objective of VUR treatment is minimizing the risk of pyelonephritis and preventing the risk for development of new renal scars with the ultimate goal of preventing renal failure (44). It is based on the risk factors of each patient, such as age, sex, grade of VUR, and presence of LUTD, breakthrough UTI, anatomical abnormalities and renal status. Patients at high risk for developing UTI or renal scars should be carefully managed.

However, the controversies persist regarding the best treatment of VUR, particularly in the choice between observation alone, CAP, endoscopic treatment or ureteral reimplantation, and, if surgical treatment is indicated, best time to perform it.

Surgical recommendations can be divided in absolute and relative indications. Absolute Recommendations include repeated UTI despite CAP, VUR that have low chance of spontaneous resolution, and preference of the parents (63, 74-76). After discussing the risks and possible outcomes with the parents, surgery should be considered if it is their will, regardless of whether it would be endoscopic injection or ureteral reimplantation. Relative Recommendations are persistence of VUR grade III to V in asymptomatic patients; presence of renal scaring, VUR grades III to V in patients with renal scars, children with difficulty to maintain clinical follow-up and to have access to health services, persistence of VUR in girls after the age of 5 years (1, 44, 75, 77-79).

Circumcision

Circumcision for children with VUR has been shown to reduce the frequency of positive urine culture although no difference was found in symptomatic UTI and changes in DMSA scan when compared to no circumcision. Its indications in children with VUR reflux should be discussed with the family.

High Grade VUR in Neonates

Severe VUR in neonates may be seen with caution. In up to 59% of cases it will improve or spontaneously resolve and should be initially managed with CAP (80, 81). Those with end stage renal disease or presenting pyelonephritis may need early surgical intervention. Options include vesicostomy, pyelostomy, and ureterostomy.

Endoscopic Treatment for VUR

Endoscopic injection of a bulking agent is the least invasive procedure for treating VUR (82) that can be indicated even before completing 1 year of life (83). There is evidence that endoscopic treatment reduces the rate of UTI compared to observation, but it is similar to CAP in short term follow-up, but presents a higher cure rate when compared to observation alone (71, 84). On the other hand, its success rate is lower than open surgery (ureteral reimplantantion), specially for high grade VUR (85).

Bulking Agents

Polymethylsiloxane (Macroplastique®): Non-absorbable. Due to the greater hardness of the material, it is necessary to use an injection gun (86-88).

Dextranomer/Hyaluronic Acid (Deflux®): Advantage of being easy to inject and with fewer complications (89). As a disadvantage, it is partially absorbed, causing loss of some volume in the long term, with recurrence of VUR in about 20% of the cases (90).

Polyalcohol/Polyacrylate (Vantris®): Not to be absorbed and easy to inject. As a disadvantage, it causes a higher inflammatory process and, therefore, has a higher risk for obstruction (91-93).

Pyrolytic Carbon (Durasphere®): Its application is difficult and there are few studies showing its effectiveness (94).

Endoscopic Treatment Technique

Subureteral injection (STING): In this technique, the injection site is about 2-3mm below the ureter orifice (at 6 o'clock) and the needle is deepened by 4-5mm (95, 96).

Hydrodistension Injection Technique (HIT): In this technique, the flow of endoscopic irrigation is positioned immediately in front of the ureteral meatus. The substance is injected approximately 5mm into the ureter. More than one injection is possible with this technique (Double HIT) (96, 97, 98).

Success rate

The higher the VUR grade the lower the success rate. Other factors related to lower success rate are LUTD, surgeon's experience, and previous injection (75, 99-101).

Postoperative follow-up

Patients should perform ultrasonography after surgery, preferably between one and three months (90, 92, 102).

Performing VCUG after the procedure is optional, and should be indicated in case of relapse of febrile UTI.

Consensus

This panel recommends the endoscopic treatment of VUR as the first surgical treatment option, except for Grade V VUR with significant ureteral dilatation.

The panel also recommends that after a second unsuccessful endoscopic injection, the possibility of treatment with open surgery should be considered. There is insufficient data in the literature to evaluate the results of re-application of Polyalcohol/Polyacrylate. Therefore, according to this panel, open surgery should be considered after failure to a first injection with this material.

If Dextranomer/Hyaluronic Acid is the bulking agent of choice, consider injecting higher volumes and use of HIT technique. If Polyalcohol/Polyacrylate is the bulking agent chosen, it is advised to use lower volumes and not use the HIT technique due to the higher risk of obstruction.

This panel recommends performing at least one annual ultrasonography, as late obstructions have been reported, especially after Polyalcohol/Polyacrylate injection.

Open surgery

Ureteral reimplantation is the most effective approach to prevent new episodes of febrile UTI, especially in high grade VUR or after unsuccessful endoscopic injection. All techniques have high success rates (>95%) (44, 75).

Complications include the possibility of obstruction (2%) and contralateral reflux (9%).

The principle of all ureteral reimplantation techniques is to create a longer submucosal tunnel, four to five times the diameter of the ureter, in an attempt to reproduce the physiological anti-reflux mechanism of compressing the ureter as

intra-vesical pressure increases with filling and urination (103).

Intra and extra-vesical procedures as well as combined techniques have been described. The choice of technique depends on the degree of dilation of the ureter, whether the reflux is unilateral or bilateral, the presence of other obstructions, and the preference of the surgeon.

The most used techniques are: Extra-Vesical: Lich-Gregoir (104).

Intra-Vesical: Cohen and Glenn-Anderson (105) and Politano-Leadbetter (106).

Bilateral extra-vesical techniques may present an increased risk of postoperative transient bladder dysfunction and urinary retention (107). In cases of unilateral VUR, the preference is for the extra--vesical approach (Litch-Gregoir technique) (2, 108).

Cohen's intra-vesical technique consists of bilateral crossing ureteral reimplantation, with the construction of a long tunnel, with a low risk of obstruction by ureter angulation. However, there is the disadvantage of possibly hindering retrograde endoscopic procedures in the future (2, 108, 109).

The combined technique of Politano-Leadbetter allows the construction of a longer tunnel, being very useful in reimplantation of a dilated ureter, but with a slightly greater risk of obstruction by angulation of the ureter. The meatus is positioned in an easily accessible position for endoscopic manipulation (2, 110).

The Glenn-Anderson technique, with intra-vesical advancement of the ureter towards the bladder neck, has a low risk of ureter angle obstruction, but presents a limit to the length of the tunnel (2).

Laparoscopic/Robotics Surgery

Laparoscopic and robotic techniques present long learning curve, even for experienced surgeons, with long operative times than open procedures. Nowadays, success rates are as high as open surgery with few complications (111-113). The main disadvantage is the cost, which is higher than any other treatment modality.

Consensus

It is the panels opinion that high grade VUR (grade V and some cases of grade IV) should be treated with ureteral reimplantation, either with open of laparoscopic/robotic techniques depending on the experience of the surgeon and the availability of the technology. In unilateral cases, extra-vesical approach should be considered while in bilateral cases, intra-vesical technique (Cohen) would be preferable.

POST-OPERATIVE FOLLOW-UP

There is no consensus regarding postoperative follow-up both in endoscopic treatment and in open, laparoscopic or robotic surgery. As the success rate of the procedures is high, it is not recommended, in general, to perform control VCUG in all patients, which should be indicated in patients with new episodes of febrile UTI and, possibly, in patients with high grade VUR treated with endoscopic procedure, where the success rate is lower.

Ultrasonography is performed between 1 and 3 months after the surgical procedure and is performed at regular intervals after endoscopic treatment because of the risk of late obstruction.

Consensus

It is the panel's opinion that a kidney and bladder ultrasound should be done after the first month of surgery to check for signs of obstruction. VCUG is indicated only in case of breakthrough UTI or after endoscopic treatment of high grade VUR.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Simultaneous bilateral native nephrectomy by retroperitoneal approach

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ABSTRACT

The indication for simultaneous bilateral native nephrectomy and the choice of surgical technique is of key importance, as these patients are burdened with a large comorbidity. The paper reports our experience of seven successful and completed simultaneous bilateral native nephrectomy procedures with retroperitoneal approach in the patient's flank position.

Seven patients (mean age 34), were indicated for the removal of both kidneys before the planned transplant. Six patients underwent haemodialysis from 48 to 84 months, and one underwent peritoneal dialysis for 60 months. Two patients had undergone graftectomy. The indications were chronic infection or hypertension. The length of the kidneys ranged from 5.8 to 10cm. All procedures were performed by the laparoscopic technique with retroperitoneal approach, with the patient in the flank position. Three trocars were used on each side. The retroperitoneal space created did not require balloon dilatation. The kidneys were removed through the 10mm trocar hole after splitting.

The duration of the procedure ranged from 150 to 240 minutes, average 139 minutes and blood loss ranged from100 to 250mL, average 142mL. There were no complications. In 6 patients, the postoperative dialysis was performed at zero-day. One patient continued peritoneal dialysis. Patients were discharged on the 2nd day, except one with peritoneal dialysis, who was discharged on the 3rd day.

Retroperitoneal laparoscopic bilateral native nephrectomy is a safe and effective technique, and it can be considered as an ideal approach for native nephrectomy. It allows for the preservation of peritoneal integrity and vessels for future vascular access.

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INTRODUCTION

In patients treated with renal replacement therapy, including those subjected to dialysis, numerous organ related complications, including kidney failure, are observed. Failures of treatment of complications within the organs by conservative methods lead to the implementation of treatment methods to remove the involved organ. The decision to undertake surgical treatment and the choice of surgical technique are of key importance, as these patients have a large comorbidity burden, which makes them particularly susceptible to complications during the postoperative period (1). Numerous methods of treatment during bilateral nephrectomy

are particularly attractive for patients with high comorbidities, including laparoscopic nephrectomy. The procedure of bilateral laparoscopic nephrectomy was first described in 1994 by Bales et al., in two patients qualified for transplantation (2). In both cases, transperitoneal access was used. The use of the laparoscopic technique results in a shorter time of hospitalization and convalescence (3-5).

This advantage is extremely important for patients undergoing dialysis because it shortens the time between kidney removal and transplantation. The next stage in the development of surgical techniques was the removal of native kidney through the retroperitoneal approach, omitting the peritoneal cavity (4-7). The choice of access, patient placement and operative technique depends on the operator's preferences. Compared to transperitoneal laparoscopic access, there appear to be several advantages to the retroperitoneoscopic approach for benign kidney disease. These advantages include ease of kidney access by developing the existing potential retroperitoneal space and avoidance of the transperitoneal approach with the resultant reduced risk of injury to and interference from intra-abdominal organs.

This article reports our experience of seven successful and completed simultaneous bilateral native nephrectomy procedures with retroperitoneal approach in the patient's flank position.

MATERIALS AND METHODS

The study consisted of 7 patients, including 4 men and 3 women between the ages of 20 and 68 (mean 34 years). All patients were undergoing long-term dialysis. Six patients underwent haemodialysis every 2 days, and one patient used peritoneal dialysis. Two patients had undergone kidney transplants and graftectomies due to rejection of the transplanted kidney. Patients were qualified for kidney removal by nephrologists if they had recurrent urinary tract infections and hypertension before the planned kidney transplant (Table-1).

Before the operation, the following routine laboratory tests were performed: morphology, ionogram, creatinine, urea, prothrombin time, international normalized ratio (INR) and activated

Table 1 - Characteristics of patients enrolled in the study.

No.	Age (years)	Gender	Dimensions of the right kidney	Dimensions of the left kidney	Dialysis type and time (months)	Indications for nephrectomy
1	30	M	10.0 x 3.2 cm	9.6 x 3.0 cm	Haemodialysis 84 months	Chronic urinary tract infection; bilateral renal calculi
2	34	M	8.2 x 3.1 cm	9.7 x 4.5 cm	Haemodialysis 48 months	Chronic urinary tract infection; bilateral staghorn calculi
3	26	F	7.5 x 3.0 cm	6.6 x 3.2 cm	Peritoneal dialysis 60 months	Chronic urinary tract infection; bilateral vesicoureteral reflux.
4	25	M	6.4 x 3.0 cm	8.1 x 3.2 cm	Haemodialysis 72 months	Hypertension; glomerulonephritis
5	28	M	7.0 x 3.5 cm	7.0 x 3.4 cm	Haemodialysis 84 months. After transplantation and graftectomy in 2008.	Hypertension; distal renal tubular acidosis
6	28	F	5.8 x 2.6 cm	6.0 x 2.4 cm	Haemodialysis 72 months	Chronic urinary tract infection; bilateral vesicoureteral reflux.
7	68	F	10.0 x 4.4 cm	17.0 x 5.8 cm	Haemodialysis 84 months. After transplantation and graftectomy in 2010.	Chronic urinary tract infection; bilateral staghorn calculi

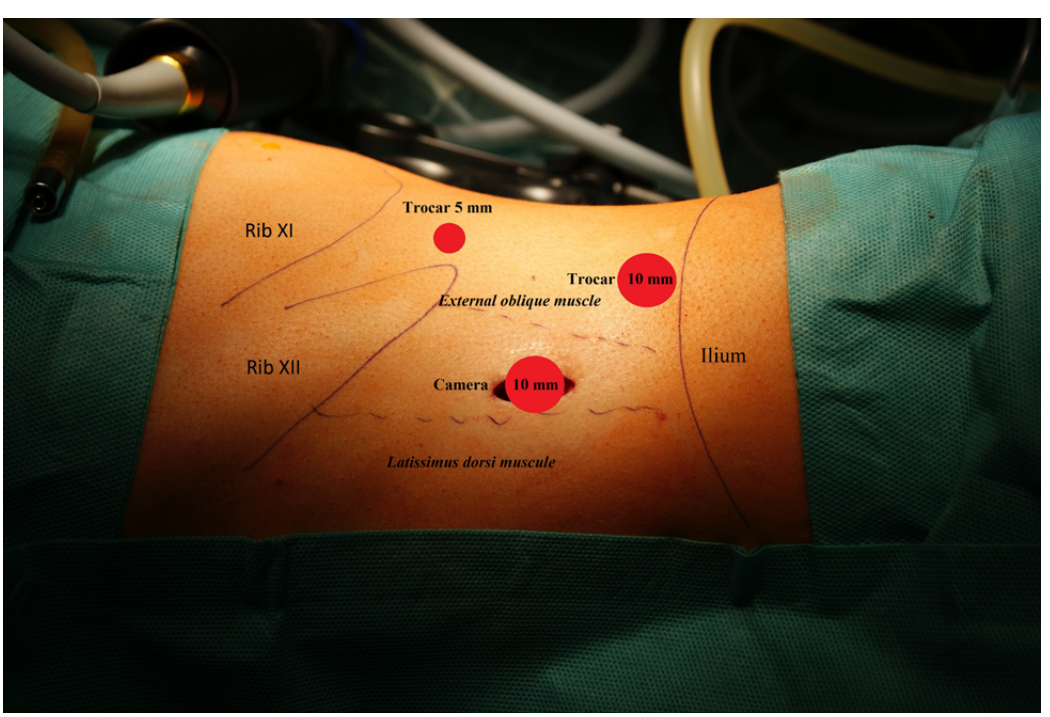
partial thromboplastin time, (APTT), ultrasound was also obtained.

On the day before the procedure, the patients underwent dialysis during the second shift in the evening. The operations were carried out the following day, early in the morning. After the procedure, all patients were transferred to the intensive care unit for monitoring of their vital signs. None patients required blood transfusions. In the zero-day period in the evening, all patients underwent hemodialysis except for one patient, who was continuing peritoneal dialysis.

All treatments were performed by a retroperitoneoscopic technique. Patients were placed in the flank position, on their side, as for classical retroperitoneal surgery. First, the right kidney was removed, because in our opinion it is more difficult. Then, after transferring the patient to the opposite side, the left kidney was removed. The treatments started with a 1cm skin incision in the upper lumbar triangle. The retroperitoneal space was created only with the trocar and optics and did not require balloon dilatation of the retroperitoneal space, which was not routinely used. Optics with an angle of inclination of 30 degrees and a diameter of 10mm were used. After introducing the first trocar with the optics and performing insufflation to 12mmHg, additional trocars were inserted under visualisation control: a 10mm trocar over the iliac plate for the right hand of the operator and 5mm under the XI rib for the left hand. Three trocars (Karl Storz SE & Co. KG, Germany) were used, 2 x 10mm and 1 x 5mm on each side. Placement of the trocars in our patients is shown in Figure-1.

All treatments were carried out in the same way. Preparation was started from visualization of the kidney cavity. First, the renal artery and vein were located. Artery and the vein were closed using hem-o-loc clips (Hem-o-lok® Ligation System, Teleflex Incorporated Earnings). After cutting the vessels, the ureter was visualized, clipped and cut. The kidney was inserted into the endoscopic bag and, after fragmentation with straight Kocher's forceps, and removed through a 1cm hole after the 10mm trocar. A drain was left in the retroperitoneal space.

Figure 1 - Scheme of patient's position with marked trocar sites. Patient placed in the left flank position during removal of the right kidney.



After removal of the right kidney, the patient was transferred to the opposite side, and the opposite kidney was removed in the same manner. Procedures on the left side were more difficult due to the presence of gas bubbles in the adipose tissue that filled the retroperitoneal space. The amount of gas was not very large, however, it slightly changed the anatomical conditions and the insight into the retroperitoneal space. The adipose tissue was loose and harder to dissect.

RESULTS

The results are presented in Table-2. There were no intra- or postoperative complications in any of the patients. We were not forced to convert the treatment to open surgery in any patients. In six patients, the first postoperative dialysis was performed in the zero-day period in the evening, and it was performed on the next one in the last patient. One patient continued peritoneal dialysis only during the entire postoperative period, without any staining of the dialysis fluid. Patients were discharged on the 2nd postoperative day, except for the peritoneal dialysis patient who was discharged on the 3rd day. All kidneys were morcellated and removed in fragments through the 10mm trocar hole.

Postoperative pathomorphological assessments showed that the microscopic picture of the kidneys was dominated by pulp atrophy, glomerulosclerosis and the proliferation of connective tissue, which are features of chronic pyelonephritis.

DISCUSSION

Retroperitoneoscopic nephrectomy is a standard technique for kidney removal in the case of benign non-functioning kidneys (8). The advantage of retroperitoneal access is surgery without the need to violate the peritoneal cavity. An inconvenience of retroperitoneal access, in the patient's position on the side, in the case of simultaneous removal of both kidneys is the need to change the position of the patient during the procedure. However, this element could be omitted. Operations that include the removal of both kidneys from a retroperitoneal approach in the patient's prone position are described and do not require a change of the patient's position (9-11).

The indications for surgery in our patients, as reported by other authors, were recurrent urinary tract infections in the course of urolithiasis, reflux and/or glomerulonephritis accompanied by difficulty to treat arterial hypertension (1, 12-17).

The specific group consisted of patients with bilateral nephrolithiasis. In our study, there were 2 patients with staghorn calculi, a significant inflammatory reaction that made the entire procedure difficult. Another group of patients consisted of those who had experienced previous rejection and removal of the graft. These patients

Table 2 - The results of the nephrectomy.

No.	Duration of the procedure	Loss of blood	Dialysis	Motor activity	Nutrition	Hospital stay
1	180 min	100 mL	Day: 0 and 1	1st day	1st day	2 days
2	240 min	160 mL	Day: 0 and 1	1st day	1st day	3 days
3	150 min	120 mL	Day: 0 peritoneal dialysis	1st day	2nd day	3 days
4	220 min	100 mL	Day: 0 and 1	1st day	1st day	2 days
5	160 min	150 mL	Day: 0 and 1	1st day	1st day	2 days
6	180 min	120 mL	Day: 0 and 1	1st day	1st day	2 days
7	240 min	250 mL	Day: 0 and 1	1st day	1st day	2 days

had extensive scars on the abdomen, which determined the choice of retroperitoneal approach.

The use of the retroperitoneal approach that does not affect the peritoneal cavity in patients prior to the planned transplant appears to be a reasonable choice. However, the operation in dialysis patients requires a specific approach. First, we do not use the balloon to create retroperitoneal space, similarly to Doublet et al. (4). As a result, no patient suffered from damage to the peritoneum or other organs. In all 7 patients, the retroperitoneal space was created only with trocar and optics, without using balloon dilatation of the retroperitoneal space. We were prompted by reduced fat tissue in dialysis patients to perform such a manoeuvre. The optics allowed the manoeuvre to create the retroperitoneal space to be carried out safely under sight control. Time was also saved. We used three trocars on each side for the procedure. After the introduction of the trocars, the preparation was started from the visualization of the kidney cavity. First, the renal pelvis, artery and vein were localized, and then, the ureter was visualized. This is not a routine procedure. Usually, the procedure of removal of the kidney begins with the visualization of the ureter and, following it, until reaching the renal pedicle. The ureter of the inactive kidney can be very narrow and might not be easily localized, which occurred in this case. The use of modifications in the form of pelvis dissection in the first stage facilitated the location of the ureter, which was then easily dissected and cut off after closing the kidney vessels. Further preparation of the kidney did not differ from the routine procedure. The operation of bilateral simultaneous removal of the kidney in patients undergoing dialysis with extra-spinal laparoscopy does not cause a higher risk than in patients without dialysis. Our operations lasted from 2.5 to 3.5 hours in total in both types of patients. During this time, we had to change the position of the patients, which was the biggest inconvenience of the procedure. The method of the retroperitoneal approach in the prone position has also been described and makes it possible to perform the procedure without changing the patient's position (9-11). This is a very interesting and remarkable proposition. However, in the work of Tanaka et al. (10), despite the lack of necessity to change the position of the patient, the operation time was much longer than ours, the operative time averaged 325min for the extirpative procedures (range 250-460 min) (10). Gundeti et al. (11) performed treatments in a shorter time of 110 to 180 min, on average 160 min, but in one patient, he was forced to convert due to peritoneal damage (11). Our procedures lasted from 150 to 240 min, on average 195 min, despite the need to change the position of the patient. We did not report any complications and did not have to convert in any of the cases. In our series of 7 patients, all patients underwent successful complete nephrectomy laparoscopically. In our study, the blood loss ranged from 100 to 250mL, average 142mL. The decrease in haemoglobin ranged from 0.1 to 1.4mg%, and no patients required transfusions. The average blood loss in the study of Tanaka was 281mL (range 15-739mL), and a patient required a transfusion (10). The result obtained by us likely results from a modification of the procedure, which deviates from the standard nephrectomy. This modification consisted of the following: resignation from the use of the balloon to create the retroperitoneal space and starting the preparation of the kidney from the cavity. We removed all the kidneys through the hole after removal of the 10mm trocar, after splitting it in the laparoscope sack. Morcellation did not significantly prolong the operation time, taking a maximum of 5 min. In most cases, we removed small kidneys from 5.8 to 8.2cm long. Two kidneys with a length of 10cm and the presence of staghorn calculi constituted a certain difficulty. The soft stones were crushed with Kocher's forceps, to the extent that they could be removed through the hole after the 10mm trocar. Morcellation allowed us to avoid widening the hole to remove the tissue. In the case of bilateral nephrectomy, the only disadvantage of the access we used was the need to change the patient's position. The inconvenience was compensated by an excellent view of the operating field, providing the opportunity to safely carry out the procedure. Similarly to other authors, we included oral intake on the first or second postoperative day (10). The technique of retroperitoneal access, in contrast to transperitoneal access, does not require preparation of the intestines, which allows quick return of

peristalsis and immediate inclusion of oral intake. The omission of the peritoneal cavity is associated with a lower probability of damage to intraperitoneal organs, and previous abdominal operations do not affect the course of the procedure. In our case, graftectomy in 2 patients did not impair the procedure. One patient with transperitoneal dialysis, due to the use of retroperitoneal technique could continue this dialysis during the entire convalescence cycle. This is undoubtedly an advantage of this technique especially in peritoneal dialysis patients (11, 18, 19). In the transperitoneal approach, this cycle would have to be postponed up to 5 days (15, 16).

Patients were hospitalized 2 days after surgery (except for 3 days in one patient with transperitoneal dialysis). Shorter stays have been described in the literature, even as short as 1 day (10) but in transperitoneal access 5.9 days (20). In our study, the hospitalization time of 2 days should be assessed as relatively short and acceptable in the context of patient safety and organizational conditions of the health care system.

A limitation of our work is the small number of patients, however, the qualification of nephrologists for simultaneous bilateral nephrectomy is also rare. Our goal was to demonstrate the safety and efficacy of the method of kidney removal through the retroperitoneal approach. Retroperitoneoscopic simultaneous bilateral nephrectomy is a well-tolerated and safe procedure for the patient. We did not report any intra or postoperative complications. The retroperitoneal approach allowed one patient to maintain peritoneal dialysis throughout the postoperative period. Furthermore, use of retroperitoneal approach in patients with indication for simultaneous removal of native kidneys gives the possibility of oral intake and, if necessary, transperitoneal dialysis on the first day. Laparoscopic bilateral nephrectomy followed by kidney transplantation is a safe and feasible alternative.

CONCLUSIONS

The retroperitoneoscopic technique appears to be particularly attractive among numerous methods used in bilateral nephrectomy for patients undergoing dialysis. Retroperitoneal laparoscopic bilateral native nephrectomy is a safe and effective technique and allows for a short hospitalization and quick convalescence. The use of retroperitoneal access allows for preserving the peritoneal integrity and vessels for future vascular access.

The technique proposed by us, that is simultaneous bilateral nephrectomy with retroperitoneal approach, with the patient's transposition and creation of retroperitoneal space, without the use of a balloon and beginning of the kidney preparation from the cavity side was safe and well tolerated in our patients. However, it should be emphasized that it requires considerable experience with laparoscopic surgery and strict adherence to several, described in our publication, technical points to ensure success. Compared to the literature data on laparoscopy in this setting, the retroperitoneoscopic nephrectomy can be considered the ideal approach for minimally invasive nephrectomy.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Elevated prostate volume index and prostatic chronic inflammation reduce the number of positive cores at first prostate biopsy set: results in 945 consecutive patients

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ABSTRACT

Objective: To assess the association between prostate volume index (PVI), and prostatic chronic inflammation (PCI) as predictors of prostate cancer (PCA). PVI is the ratio between the central transition zone volume (CTZV) and the peripheral zone volume (PZV).
Materials and methods: Parameters evaluated included age, prostate specific antigen (PSA), total prostate volume (TPV), PSA density (PSAD), digital rectal exam (DRE), PVI, PCI and number of positive cores (NPC). All patients underwent baseline 14-core, transperineal random biopsies. Associations of parameters with the NPC were investigated by univariate and multivariate linear regression analysis.
Results: Between September 2010 to September 2017, 945 patients were evaluated. PCA was detected in 477 cases (50.7%), PCI in 205 cases (21.7%). PCA patients, compared to negative cases, were older (68.3 vs. 64.4 years) with smaller TPV (36 vs. 48.3mL) and CTZV (19.2 vs. 25.4), higher PSAD (0.24 vs. 0.15ng/mL/mL), further PVI values were lower (0.9 vs. 1.18) and biopsy cores less frequently involved by PCI (9.4% vs. 34.2%). High PVI and the presence of PCI were independent negative predictors of NPC in model I considering PSA and TVP (PVI, regression coefficient, RC -0,6; p=0.002) and PCI (RC -1,4; p <0.0001); and in model II considering PSAD (PVI:RC -0,7; p <0,0001; and PCI: RC -1,5; p <0.0001).
Conclusions: High PVI and the presence of PCI lowered the mean rate of NPC and is associated with less aggressive tumor biology expressed by low tumor burden. PVI can give prognostic information before planning baseline random biopsies. Confirmatory studies are required.

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INTRODUCTION

At present, prostate cancer (PCA) is a worldwide major health problem and is closely related to the male aging process (1). In daily practice, suspicion of PCA is a hard task for the urologist who is challenged to exclude or confirm the diagnosis by planning baseline random biopsies

including cores taken from the apex to the base of the gland. Efforts have been applied in order to avoid unnecessary biopsies that represent the major drawback of this practice. Systematic baseline prostate biopsies give specific information of the microenvironment of the gland. When PCA is detected, positive cores are evaluated for site, zone, number, percentage of cancer involvement and tumor grade. As a result, clinical and pathological features allow tumor staging and classification of patients into classes with consequences on management because of their prognostic potential (1). On the other hand, histology of negative cores shows typical features including prostatic chronic inflammation (PCI), high grade intraepithelial neoplasia, glandular atrophy or hyperplasia (1).

Benign prostatic enlargement (BPE), which is histologically supported by a pattern of benign prostatic hyperplasia (BPH), PCI and PCA are diseases associated with aging. PSA is a useful marker for assessing total prostate volume (TPV), prostatic growth rate and PCA risk. Also, imaging evaluation of the prostate by measuring the volume is important when treating BPH by 5α-reductase inhibitors. So far DRE, PSA and prostate size are important parameters for assessing prostate diseases (1, 2). However, the detection of abnormal findings will lead to the suspicion of PCA. A normal digital rectal exam (DRE) with prostate specific antigen (PSA) between 2 to 10ng/dL might suggest further investigations such as new biomarkers and imaging modalities in order to avoid unnecessary biopsies. Although promising, novel biomarkers do not show enough evidence to recommend their use in clinical practice, moreover, multiparametric resonance imaging (mp-MRI) should not be performed on baseline biopsies (1, 2). In order to avoid unnecessary baseline biopsies, it is pivotal to assess clinical factors that associate with positive or negative cancer outcomes. Although PSA density (PSAD) has shown a positive association with the risk of PCA, especially in patients with PSA levels of 4-10ng/mL, it has limited predictive power because it closely depends on distributions of prostate volumes (1, 3).

PCI has been classified into four categories by the National Institutes of Health (4). The last category, which is coded type IV, is detected after biopsy in patients who have no history of genitourinary tract pain complaints but present with increased levels of prostate-specific antigen (PSA) and/or abnormal digital rectal exam (DRE). Although the association between PCI and PCA is controversial, the majority of studies have shown that PCI reduces the risk of PCA (5).

In patients undergoing baseline prostate biopsies, our working group has demonstrated that PCI is inversely associated with the risk of PCA (6-12). Moreover, our group has also investigated the associations of prostate volume index (PVI), defined as the ratio of the volume of the central transition zone (CTZV) to the volume of the peripheral zone (PZV) of the prostate, with the risk of PCA and the outcomes have shown an inverse association (7, 13, 14).

The aim of this study was to evaluate both PVI and PCI as predictors of the number of positive cores in patients undergoing baseline biopsies.

MATERIALS AND METHODS

The study had Institutional Board Review approval. All patients signed informed consent for using the data. Data of 1.910 patients were retrospectively evaluated during a period running from September 2010 to September 2017. The study evaluated patients elected to baseline random biopsies with PSA levels less than 30µg/L. Indications to perform biopsies were increased PSA levels, abnormal DRE or abnormal imaging of the prostate. Baseline biopsies were systemically taken in different zones of the gland according to the standard pattern including 14 cores. Analysis of adjunctive targeted cores were excluded in order to avoid skewing phenomena. Indications to perform prostate biopsies included increased PSA levels, abnormal DRE, increased PSA with abnormal DRE, and abnormal imaging findings.

Each patient was evaluated for age (years), body mass index (BMI, kg/m^2), PSA (ng/L), DRE findings that were coded as normal or abnormal. Total volume of the prostate (TPV) and central transition zone volume (CTZV) were directly measured before biopsy by transrectal ultrasound (TRUS). In both cases, volume was measured by the formula for an ellipsoid [diameter1 x diem-

eter2 x diameter3 x 0.52] and transformed into volume (mL). The volume of the peripheral zone of the prostate (PZV) was measured by subtracting CTZV from TPV and PVI was calculated as the ratio of CTZV on PZV. PSAD was calculated as ratio of total PSA on TPV.

Each core was evaluated by our dedicated pathologist who systematically assessed the following features: (i) length (mm); (ii) ISUP tumour grade group; (iii) number of positive cores (from zero to 14); (iv) percentage of cancer involving each core; (v) prostatic Intraepithelial neoplasia (PIN); (vi) PCI; (vii) glandular atrophy; (viii) atypical small acinar cell proliferation. Features considered in this analysis were ISUP tumour grade group, number of cores involved by cancer and PCI was defined as type IV according to the definition of National Institutes of Health (4).

The aim and design of the study was to investigate, at baseline biopsies, the association of PVI and PCI, among other factors, with the prostate cancer extension assessed as tumour volume which was evaluated by considering the number of positive cores that ranged from zero (cores without cancer) to 14 (all cores involved by cancer). The number of cores sampled was not increased as total prostate volume increased.

STATISTICAL METHODS

Summary statistics of population and subpopulations with or without the PCA were computed. Continuous variables were evaluated as means with relative standard deviations. Categorical factors were evaluated as frequencies with relative rates. Because of the non-normal distribution, continuous factors were transformed into natural logs in order to assess differences between groups and to compute linear regression analysis.

Differences of factors between groups were assessed by Student's t test for continuous variables and by Chi squared test or Fisher's exact test as appropriate for categorical factors. The association of factors with tumour extension was assessed by univariate and multivariate linear regression models considering the several factors as predictors of the NPC. Because of the high correlation between PSA, TPV and PSAD, two multivariate models were considered. Bivariate clinical models including PVI were computed. The software used to run the analysis was IBM-SPSS version 20. All tests were two-sided, with a significance level of $p < 0.05$.

RESULTS

We evaluated 945 patients who met the inclusion criteria of the study. Statistics of the different parameters is reported in Table-1. Percentages of negative and positive cores are depicted in Figure-1. Overall, PCA was detected in 477 cases (50.7%) and the mean number of positive cores (NPC) was 4.7. The distribution of factors was significantly different ($p < 0.0001$) between subgroups with or without PCA except for BMI ($p=0.536$). PCA patients, when compared to negative cases, were older (68.3 vs. 64.4 years) with higher PSA levels (7.8 vs. 6.6ng/mL), lesser prostate enlargements (lower measurements of TPV: 36 vs. 48.3mL, CTZV: 19.2 vs. 25.4, PZV: 19.2 vs. 22.), higher PSAD (0.24 vs. 0.15ng/mL/mL) and abnormal DRE more frequently detected (41.7 vs. 23.3); moreover, PVI values were lower (0.9 vs. 1.18) and cores less frequently involved by PCI (9.4% vs. 34.2%).

Analysis of univariate and multivariate linear models are reported in Table-2. On univariate analysis, all regression coefficients (RC) with relative 95% confidence intervals were significant predictors of the NPC. The regression coefficients were positive for Age (RC 5.8; $p < 0.0001$), PSA (RC 1.3; $p < 0.0001$) and DRE (RC 2.2; $p < 0.0001$), but negative for TPV (RC -2.1; $p < 0.0001$), PVI (RC -1.3; $p < 0.0001$) and PCI (RC -2,1; $p < 0.0001$). On multivariate analysis, two models were computed with model I including Age, PSA, TPV, PVI, DRE and PCI as well as model II considering Age, PSAD, PVI, DRE and PCI. In both models, all factors were independent predictors of the NPC. In model I, regression coefficients resulted positive for Age (RC 4.4; $p < 0.0001$), PSA (RC 1.8; $p < 0.0001$), DRE (RC 1.7; $p < 0.0001$), but negative for TPV (RC -2.1; $p < 0.0001$), PVI (RC -0.6; $p=0.002$) and PCI (RC -1.4; $p < 0.0001$). Also, in model II, regression coefficients were positive for Age (RC 4.3; $p < 0.0001$), PSAD (RC 1.9; $p < 0.0001$), DRE (RC 1.8; $p < 0.0001$),

Table 1 - Statistics of factors in patients undergoing baseline biopsies.

Factors	Population	Negative cores	Positive cores (^)
n (%)	945	468 (49,5)	477 (50,7)
Age, years			
mean (SD)	66.4 (8.3)	64.4 (8)	68.3 (8.1)
Body mass index (BMI), kg/m²			
mean (SD)	26.4 (3.2)	26.3 (3.3)	26.5 (3.1)
Prostate specific antigen (PSA), ng/mL			
mean (SD)	7.2 (4.5)	6.6 (3.8)	7.8 (5)
Total Prostate Volume (TPV), mL			
mean (SD)	42.1 (20.2)	48.3 (22.4)	36 (15.4)
Central Transition Zone Volume (CTZV), mL			
mean (SD)	21.1 (13.5)	25.4 (15.6)	16.8 (9.3)
Peripheral Zone Volume (PZV), mL			
mean (SD)	21 (8.9)	22.8 (9.4)	19.2 (7.9)
PSA Density (PSAD), (ng/mL)/mL (*)			
mean (SD)	0.19 (0.14)	0.15 (0.09)	0.24 (0.17)
Prostate Volume Index (**)			
mean (SD)	1.04 (0.82)	1.18 (1.08)	0.90 (0.40)
Digital Rectal Exam (DRE), n (%)			
normal	637 (67.4)	359 (76.7)	278 (58.3)
abnormal	205 (21.7)	109 (23.3)	199 (41.7)
Prostatic Chronic Inflammation (PCI), n (%)			
absent	740 (78.3)	308 (65.8)	432 (90.6)
present	205 (21..7)	160 (34.2)	45 (9.4)
ISUP grade group			
1			234 (49.1)
2			110 (23.1)
3			72 (15.1)
4			36 (7.5)
5			25 (5.2)
Number of Positive Cores (NPC)			
mean (SD)			4.7 (3.2)

(^) for prostate cancer; (*); ratio of PSA on TPV; (**), ratio of CTZV on PZV; (^), all tests comparing the two groups were significant except for BMI; SD: standard deviation

Figure 1 - ercentages of negative and positive cores in 945 patients who underwent standard baseline trans-perineal biopsies because of suspected prostate cancer.

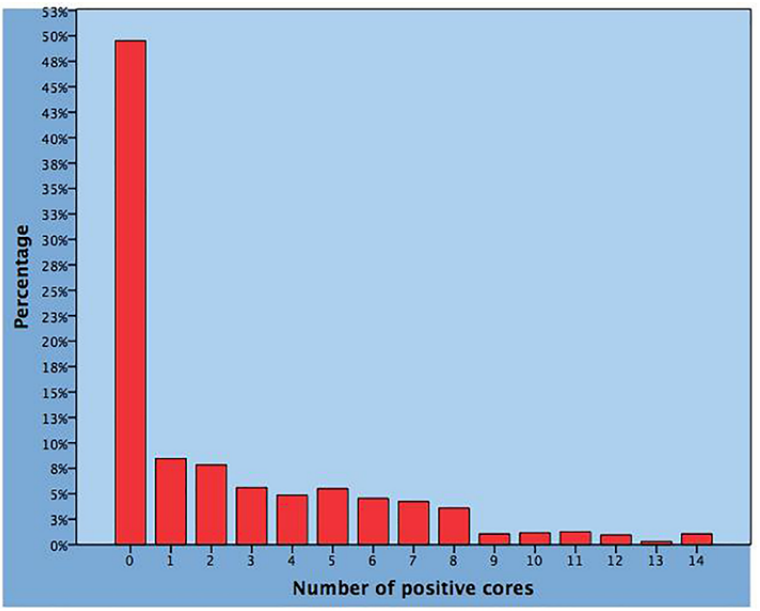


Table 2 - Linear regression models of factors predicting the number of positive cores at baseline biopsies in 945 cases.

	Univariate model		Multivariate model (I)		Multivariate model (II)	
Factors	Regression coefficients (95%CI)	P-value	Regression coefficients (95%CI)	P-value	Regression coefficients (95%CI)	P-value
Age (*)	5.8 (4.2 ; 7.4)	<0,0001	4.4 (3.1 ; 5.8)	<0.0001	4.3 (2.9 ; 5.7)	<0.0001
PSA (*)	1.3 (1.0 ; 1.7)	<0.0001	1.8 (1.5 ; 2.1)	<0.0001		
TPV (*)	-2.1 (-2.6 ; -1.7)	<0.0001	-2.1 (-2.6 ; -1.7)	<0.0001		
PSAD (*)	2.1 (1.8 ; 2.3)	<0.0001			1.9 (1.6; 2.2)	<0.0001
PVI (*)	-1.3 (-1.7 ; -0.8)	<0.0001	-0.6 (-1.0 ; -0.2)	0.002	-0.7 (-1.1 ; -0.4)	<0.0001
DRE						
normal	Ref		Ref		Ref	
abnormal	2.2 (1.7 ; 2.5)	<0.0001	1.7 (1.4 ; 2.1)	<0.0001	1.8 (1.4 ; 2.2)	<0.0001
PCI						
absent	Ref		Ref			
present	-2.1 (-2.5 ; -1.5)	<0.0001	-1.4 (-1.9 ; -1.1)	<0.0001	-1.5 (-1.9 ; -1.1)	<0.0001

See also Table 1; (*) factor evaluated as natural log; CI. confidence intervals

but negative for PVI (RC -0.7; p <0.0001) and PCI (RC -1.5; p <0.0001). The regression coefficients of PVI and PCI, although decreased when compared to the univariate model, resulted both independent predictors of the NPC.

Table-3 shows bivariate clinical models of factors predicting the mean NPC. In each model, PVI, evaluated as a continuous variable, is combined with a clinical factor which is stratified into quartiles with the first quartile

Table 3 - Bivariate linear regression models of factors predicting the number of positive cores.

Factors	Regression coefficients (95% CI)	*P-value*
PVI (*)	-1.4 (-1.8 ; -1.1)	<0.0001
Age by quartiles (**)		
<62	Ref	
62-67	0.7 (0.2 ; 1.3)	0.007
68-72	1.1 (0.5 ; 1.7)	<0.0001
>72	2.1 (1.5 ; 2.7)	<0.0001
PVI (*)	-1.4 (-1.9 ; -1.1)	<0.0001
PSA by quartiles		
<4.8	Ref	
4.8 - 6.2	0.2 (-0.2 ; 0.8)	0.332
6.3 - 8.4	0.3 (-0.2 ; 0.9)	0.223
>8.4	2.0 (1.4 ; 2.6)	<0.0001
PVI (*)	-0.7 (-1.1 ; -0.2)	<0.0001
TPV by quartiles		
<28.2	Ref	
28.2 - 37.9	-0.7 (-1.2 ; -0.1)	0.016
38 - 51.5	-1.3 (-1.9 ; -0.7)	>0.0001
>51.5	-2.1 (-2.6 ; -1.4)	<0.0001
PVI (*)	-0.7 (-1.2 ; -0.3)	<0.0001
PSAD by quartiles		
<0.12	Ref	
0.12 - 0.16	0.6 (0.1 ; 1.1)	0.023
0.17 - 0.23	1.2 (0.7 ; 1.7)	<0.0001
>0.23	3.5 (2.9 ; 4.1)	<0.0001
PVI (*)	-1.2 (-1.5 ; -0.7)	<0.0001
DRE		
normal	Ref	
abnormal	2.0 (1.6 ; 2.4)	<0.0001
PVI (*)	-1.1 (-1.4 ; -0.6)	<0.0001
PCI		
absent	Ref	
present	-1.8 (-2.3 ; -1.4)	<0.0001

See also Table 1; (*) evaluated by natural logs

as reference. In each model, PVI decreases the mean rates of NPC. Considering positive predictive factors along groups, the mean NPC was increased by Age, PSAD, abnormal DRE and PSA, but only for values above the third quartile (PSA >8.4ng/mL). Evaluating negative predictors along quartiles, the mean NPC was decreased by TPV and PCI. The association of mean NPC with PSAD (positive) and PVI quartiles (negative) is depicted in Figure 2. Finally, Figure-3 shows that the presence or absence of PCI decreases or increases the mean NPC along PVI quartiles.

Figure 2 - Bivariate model predicting the mean number of positive cores by prostatic specific antigen density (PSAD) and prostate volume index (PVI) quartiles.

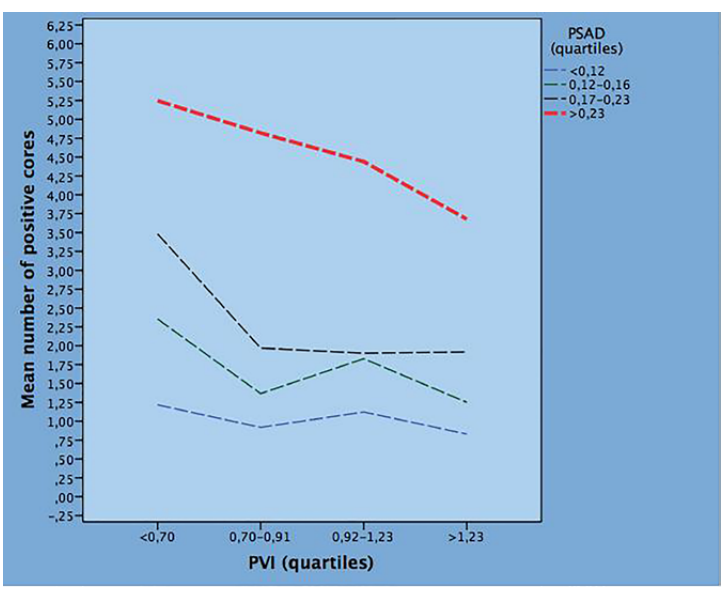
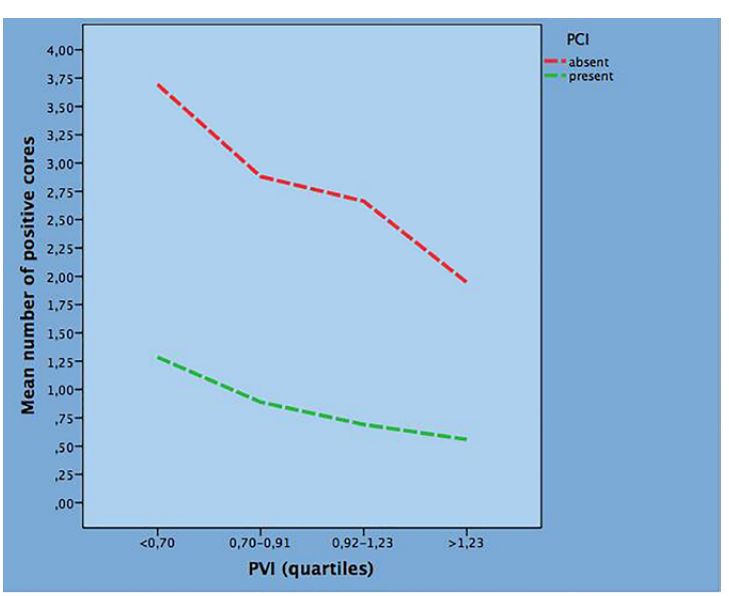


Figure 3 - Bivariate model predicting the mean number of positive cores by prostatic chronic inflammation (PCI) and prostate volume index (PVI) quartiles.

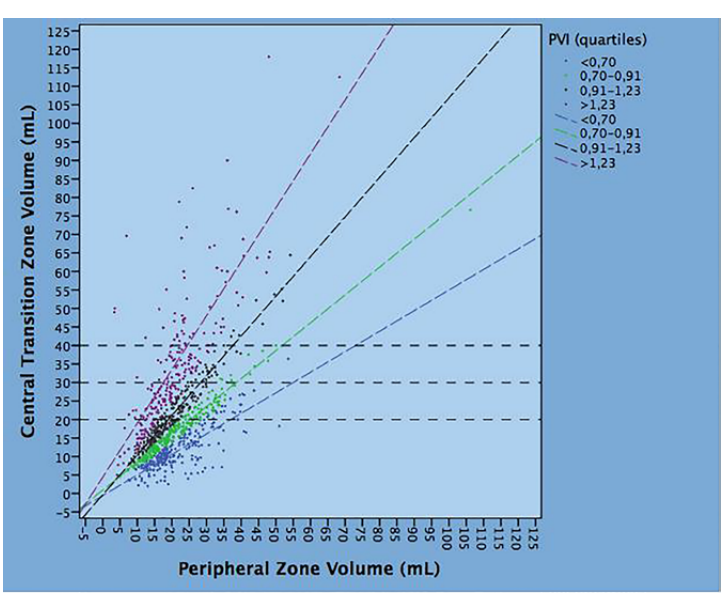


DISCUSSION

BPH and PCA are age related disease which may be both present when evaluating patients (1, 2). Abnormal clinical findings trigger baseline biopsies because PCA is suspected. When PCA is ruled out, tumor grade and intra-prostatic tumor load are pivotal parameters for classifying patients into risk categories which impact on management decisions. In the low and intermediate risk categories, tumor burden, which is evaluated as stage T1c or T2 (a/b), is a critical issue because cancer biology is not properly assessed as documented by high upstaging and upgrading rates after radical prostatectomy. Age, abnormal DRE, PSA, TPV and PSAD are known factors that associate with PCA risk at baseline biopsies, moreover, each factor relates to tumor load (1).

The prostate volume has been demonstrated to have an inverse correlation with prostate cancer risk (15-20). In our study, we focused on evaluating all these factors together with PVI in order to evaluate tumor biology which was assessed as tumor load by the NPC. NPC was independently decreased by PVI indicating inverse association between PVI and tumor load. This finding was expected since we have previously shown that PVI associated with a decreased risk of PCA at baseline biopsies (7, 13, 14). So far, PVI associated with a decreased risk of PCA and decreased NPC in patients undergoing baseline biopsies indicating inverse association with tumor biology. PVI is a pure measure since represents a ratio between volumes. We have shown that PVI represents the gradient of the regression line of TZV as a function of PZV (7, 13, 14). Considering the relations between PZV and TZV, PVI quartiles represent the different gradients of the regression lines between the two volumes. This is illustrated in Figure-4 which shows the regression lines of TZV as a function of PZV. As shown, the patients are classified into 4 groups according to PVI quartiles. The different relations between volumes are outlined along different PVI quartiles. As an example, when TZV is measured 40mL, the mean PZV is 20mL for PVI >1.23, 38 for PVI between 0.91-1.23, 5, 52 for PVI between 0.70-0.91 and 75 for PVI <0.70; so far, when TZV is fixed constant, PZV increases along decreasing PVI quartiles. This indicates that, for fixed values of TZV, the mean rates of NPC are increasing for increasing values of PZV which decreases PVI, as shown by the results of the study. Our findings suggest that TPV is not to be considered just a measure but the sum of

Figure 4 - The regression lines of the transitional zone volume (TZV) as a function of the peripheral zone volume (PZV). The patients are classified into 4 groups according to PVI quartiles. The different relations between volumes are outlined along different PVI quartiles.



a combination of non-homogenous volumes including the two main zones of the prostate.

The dynamics of the two zonal volumes, CTZV and PZV, change with time indicating a close association with aging and PCA risk. These findings suggest a new way to approach the subject of dealing with the biology of tumors of the prostate gland. The inverse association of PVI with PCA biology may be explained by theories suggesting associations between growth and differentiation of the prostate. During the aging process, CTZV and PZV of the prostate are exposed to different levels of androgenic activity such as total testosterone which determine different dynamics on volume growth rates. In theory, higher testosterone activity in the PZV might trigger larger growth rates than CTZV leading to decreased PVI values. Moreover, since the peripheral zone is being exposed to higher testosterone levels, tumors with more aggressive biology are expected to occur in this zone. This hypothesis is supported by findings showing positive association between preoperative total testosterone levels more aggressive tumors in radical prostatectomy specimens (21-23).

Also, there may be an increased chance of accurately targeting a cancer lesion in patients with smaller prostates when compared to patients with larger prostates with similarly sized lesions. This may also be the reason why lower cancer detection rates are reported in patients with large prostates. However, this theory is in contention and has not been proven in the literature (24), therefore in our clinical practice we did not increase the number of biopsy cores according to the prostate volume.

Importantly, although there has been a recent increase in the utilization of prostatic MRI in the last few years, (25) TRUS is a more cost-effective and widely-available imaging modality that can be used to evaluate the prostate volume in primary, secondary and tertiary centers. On the other hand, TRUS volume evaluation using the ellipsoid formula has been related to 15% intra-observer variability and 93% reliability, as well as 22% of inter-observer variability and 87% inter-observer reliability (26).

When planning baseline biopsies because of suspected cancer, high rates of negative cases are to be expected, moreover, negative cancer outcomes arise the unsettled issue of how to avoid unnecessary biopsies (1, 2). It has been shown that large prostates are an increased risk of unnecessary biopsies because they associate with higher PSA values at diagnosis (19). Moreover, prostatic chronic inflammation type IV is also a feature of unnecessary baseline biopsies because the condition associates with both increased PSA levels and/or abnormal DRE (4). Literature reviews on this subject have shown that the risk of PCA is reduced when PCI is present in prostate microenvironment (5, 27). Our group has shown that PCI associates with a reduced risk of PCA at baseline biopsies (6-12). In the present study, we wanted to test the hypothesis that the presence of PCI in prostate microenvironment could associate with less aggressive tumor biology. The results showed that the mean rate of NPC was decreased when PCI, which represented 21% of the population, was detected in biopsy cores. This result was expected after we have shown the inverse association between PCI and tumor biology defined by ISUP grade groups (12). An unexpected and surprising finding was that both PVI and PCI independently decreased the mean rate of NPC. So far, PCI inversely related to PCA biology because it associated with less extensive tumor load independently by PVI measurements. These findings are depicted in Figure-3 which shows the phenomena involving PVI and PCI in PCA biology. It is interesting to speculate on hypotheses explaining the negative association between PCI and PCA. As a theory, PCI might be actively involved in the early steps of PCA by inducing the differentiation of antitumorigenic cellular phenotypes by the immune system in prostate microenvironment (28, 29). We have hypothesized cellular signalling pathways between PCI and PCA (6-12). Briefly, during the first steps of carcinogenesis, high grade PIN interrupts the basement membrane with diffusion of cancer cells that induce recruitment of immune cells by producing inflammatory factors and cytokines. Going on with this patterns, tumor antigens are exposed to lymphocytes which include both the helper (CD4+) and cytotoxic (CD8+) phenotypes which cooperate to each other in order to kill the early transformed cancer cells. The result

is that cancer progression is impaired or slowed down by the activated immune system.

We have also shown that PCI is related to prostate volumes as well as PCA (11). The association of PCI was positive with CTZV and negative with PCA. In the present study we have shown that increasing PVI measurements decreased the NPC indicating inverse association with aggressive tumor biology. We may speculate interactions between PCI and CTZV growth rates which are mediated by biological factors produced by inflammatory cells, total testosterone and estradiol intra-prostatic levels. Interactions and variations among these factors may induce and accelerate CTZV growth rates which prevail on those ongoing in the PZV which is compressed by the expanding CTZV. Rapid and increasing growth rates involving CTZV increase PSA production which leads the clinician to plan baseline biopsies which are less likely to be positive or to have an aggressive biology in prostates harboring these features. Controlled studies are required in order to verify these hypotheses on biology of prostate volumes, PCI and PCA.

In clinical practice, total PSA is an important parameter for assessing prostate diseases because it relates to prostate volumes, cancer and chronic inflammation; moreover, PSAD has a limited power in predictive PCA because it is closely related to prostate volumes (1, 2, 19). So far, increased PSA values may be sustained by one or more of these conditions. In our study, we have shown that although continuous PSA was an independent predictor of NPC, only values above the third quartile (PSA >8.4ng/mL) significantly associated with tumour extension (Tables 2 and 3), interestingly, the mean rate of positive cores decreased from 6 to 2 when PVI increased from the first to the third quartile in this set of patients. PSA measurements below the fourth quartile did not predict NPC because these values might be related to prostate volumes and/or chronic inflammation, moreover, it is possible that the fraction of PSA related to tumor load was so low that it did allow significant predictive value. On the contrary, we suppose that PSA values >8.4 were predictive because they associated with higher tumor burden as shown by the mean NPC.

All these findings are more important considering that in our previous experience we demonstrated that the NPC is strongly associated with more aggressive PCA resulting in tumor upgrading and upstaging, unilateral or bilateral lymph node metastasis and seminal vesical invasion (30-34).

These results should be considered in clinical practice in order to avoid unnecessary baseline biopsies.

Our study has many strengths. First, it represent the results of a single center in which cores were evaluated by a single dedicated pathologist. Second, all biopsies were baseline and taken in a standard fashion with the standard number of 14 cores which were random and representing different coded zones of the prostate. Third, the analysis did not consider targeted cores in order to avoid skewing phenomena. Fourth, TPV and CTZ volumes were measured in standard fashion in each patient by trained urologists in performing trans-perineal prostate biopsies. Fifth, PCI was investigated in each core in a standardized fashion as reported in the methods section. Sixth, the parameters assessed are useful for evaluating tumor extension by the NPC.

However, our study also has several limitations. First, because it was retrospective and not prospective, it has all the limits related to such kind of studies. Second, prostate volume evaluations were performed using ellipsoid -TRUS method that has been demonstrated to have a non-negligible intra and inter observer variability (26). Third, because prostate volumes were not compared to prostate weights in radical prostatectomy specimens, measured prostate volumes might not reflect the true values of prostate sizes. Fourth, tumor extension was not compared to PCA volume in radical prostatectomy specimens. Fifth, larger prostates with higher PSA levels might undergo biopsy more frequently than smaller prostates with lower PSA levels and this might be a bias. Fifth, PCI was not graded and inflammatory cells were not qualitatively assessed for immunologic components. Finally, comparative studies are missing.

CONCLUSIONS

In patients undergoing baseline prostate biopsies, PVI and PCI decreased the number of

positive cores and associated with less aggressive tumor biology expressed by lower tumor extension inside the gland. PVI is a parameter to be considered before planning baseline random biopsies. Confirmatory studies are required.

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.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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Antonio B. Porcaro and Alessandro Tafuri contributed similarly as first author

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Comparison of pain levels in fusion prostate biopsy and standard TRUS-Guided biopsy

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ABSTRACT

Objectives: Fusion prostate biopsy (FPB) has recently emerged as a popular and successful biopsy technique on diagnosis of prostate cancer. The aim of this study was to compare the pain levels in TRUS-guided standard 12-core prostate biopsy (SPB) and MpMRI-guided FPB.
Materials and Methods: Patients detected with a PI-RADS (Prostate Imaging Reporting and Data System) ≥3 lesion on MpMRI underwent MpMRI-guided FPB (Group I) and the patients who had no suspected lesions or had a PI-RADS <3 lesion on MpMRI underwent TRUS-guided SPB (Group II). Pain assessment was performed using Visual Analog Scale (VAS) five minutes after the procedure. Following the procedure, the patients were asked to indicate the most painful biopsy step among the three steps.
Results: 252 patients were included in this study (Group I=159, Group II=93). The mean number of cores and the malignancy detection rate were significantly higher in Group I compared to Group II (p <0.001, p=0.043, respectively). No significant difference was found between the two groups with regard to VAS scores (p=0.070). The most painful part of the whole procedure was revealed to be the insertion of the probe into the rectum. However, no significant difference was found between the two groups with regard to the most painful biopsy step (p=0.140).
Conclusion: FPB, with a relatively higher cancer detection rate, leads to the same pain level as SPB although it increases the number of biopsy cores and involves a more complex procedure compared to SPB. Further prospective studies with larger patient series are needed to substantiate our findings.

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INTRODUCTION

Prostate cancer is the second most common cancer in men (1). Common procedures performed in the treatment of prostate cancer include digital rectal examination (DRE) and the serum prostate-specific antigen (PSA) test (2).

Periprostatic nerve block (PNB) is one of the most common and effective anesthetic techniques used for pain management during transrectal ultrasound (TRUS)-guided standard 12-core prostate biopsy (SPB) (3, 4). Additionally, intrarectal administration of anesthetic drugs has also been shown to reduce the pain level during biopsy (5,

6). In the past, prostate biopsies performed without these methods had caused serious difficulties for clinicians and patients. Although analgesia and anesthesia methods used today decreased pain significantly, patients continue to experience some pain (7, 8).

Multiparametric magnetic resonance imaging (MpMRI)-guided fusion prostate biopsy (FPB) has recently emerged as a popular technique with the aid of technological advancements. Despite involving a more complex procedure compared to SPB, this technique has been shown to provide successful outcomes in numerous studies (9-11). In this technique, unlike in SPB, additional biopsy cores beside 12 biopsy cores are obtained from the suspicious lesions detected on MpMRI (12).

In this study, we aimed to compare the pain levels in the patients that underwent TRUS-guided SPB and MpMRI-guided FPB in our clinic.

MATERIALS AND METHODS

Patients

This prospective study included patients that underwent prostate biopsy due to suspected prostate cancer at Department of Urology, Erciyes University, between December 2016 and January 2019. Patients detected with a PI-RADS (Prostate Imaging Reporting and Data System) ≥3 lesion on MpMRI underwent MpMRI-guided FPB (Group I) and the patients who had no suspected lesions or had a PI-RADS <3 lesion on MpMRI underwent TRUS-guided SPB (Group II). Patients with a previous negative biopsy, neurological disorders that could affect the pain level such as paraplegia or hemiplegia, and a serum total PSA level of >50ng/mL were excluded from the study. Moreover, patients that used analgesics for any reason on the day of or the day before the procedure, underwent biopsy under general anesthesia, and had such diseases as anal fissure or hemorrhoidal disease that could alter the pain threshold were also excluded from the study.

Pre-biopsy procedure

Appropriate antibiotic prophylaxis was performed in each patient based on the results of rectal swabbing administered before the biopsy procedure. No bowel preparation or rectal cleansing was administered prior to the procedure. A MpMRI scan was performed without an endorectal coil in each patient (Siemens, Magnetom, 1.5 T).

Local anesthesia

Initially, 2% lidocaine gel was applied to the anal cavity of each patient. After waiting for 10 minutes, the ultrasound probe was introduced into the rectum and PNB was performed by infiltrating 5mL 2% prilocaine (VEM Medicine, Istanbul, Turkey) diluted 1:1 into the angle between the seminal vesicle and base of the prostate in the parasagittal plane with an 18-gauge (G) and 30-centimeter (cm) needle.

Biopsy procedure and pain assessment

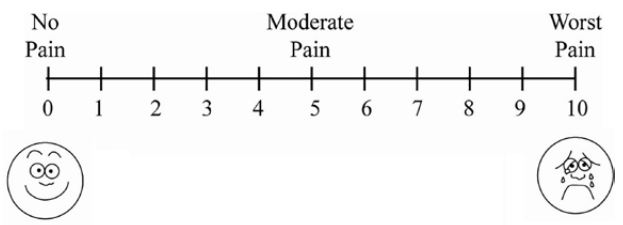
TRUS-guided SPB was performed by obtaining 10-12 core samples in each patient. FPB was performed by obtaining 10-12 core samples in each patient, followed by the acquisition of 2-4 core samples for each suspected lesion detected on MpMRI (combined biopsy). All the biopsy procedures were performed using an ultrasound (US) fusion device based on rigid registration (Logiq E9, GE, USA) with an endorectal single-angle probe (type: IC5-9-D).

Prior to the biopsy procedure, each patient was verbally informed about the three biopsy steps (1: insertion of the probe into the rectum, 2: probe manipulation, and 3: the piercing of the biopsy needle) and were asked to indicate the most painful step for them after the procedure. Following the procedure, pain assessment was performed using Visual Analogue Scale (VAS) (13). VAS is a self-reporting measure of pain intensity consisting of a 0-10 scale, whereby 0 indicates no pain and 10 indicates the most severe and intolerable pain (Figure-1).

Data collection and statistical analysis

Patient data regarding age (years), body mass index (BMI), serum PSA levels, prostate volumes measured during the procedure, total number of cores obtained by biopsy, VAS scores, the most painful biopsy step, and histopathological examination results were recorded for each patient. Prostate volume was measured following the

Figure 1 - Visual Analog Scale.



administration of PNB using the following formula: Height x Width x Length x 0.523.

Statistical analyses were performed using IBM SPSS 22.0 (Armonk, NY: IBM Corp.). Normal distribution of data was analyzed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive data were expressed as mean±standard deviation (SD) or median (25th-75th percentile) based on the distribution pattern of the data. Variables with normal distribution were compared using Independent Samples t-test. Quantitative variables with non-normal distribution and independent groups with ordinal data were compared using Mann-Whitney U test. Categorical variables were compared using Chi-square test. A p value of <0.05 was considered significant.

Ethical approval

In this study, written and verbal consent was obtained from the patients for biopsy and study procedures. The study was approved by the Erciyes University Clinical Research Ethics Committee (Approval No. 2014-508).

RESULTS

The study included a total of 252 patients, comprising 159 (63.1%) patients that underwent FPB (Group I) and 93 (36.9%) patients that underwent SPB (Group II). Mean age was 61.99 (±6.95) years, median BMI was 26.10 (22.80-28.20) kg/m^2, median serum PSA level was 7.28 (5.00-9.57) ng/dL and median prostate volume was 50.00 (36.92-65.00) mm3 in 252 patients.

No significant difference was found between the two groups with regard to age, BMI, serum PSA levels, and prostate volumes (p=0.612, p=0.966, p=0.615, p=0.627, respectively). However, the median number of cores and the malignancy detection rate were significantly higher in Group I compared to Group II (p <0.001, p=0.043, respectively) (Table-1).

No significant difference was found between the two groups with regard to VAS scores (p=0.070) (Table-2). The most painful part of the whole procedure was revealed to be the insertion of the probe into the rectum (Table-2). However, no significant difference was found between the groups with regard to the most painful biopsy step (p=0.140).

DISCUSSION

Our results suggested that FPB, when administered with an effective anesthetic technique, causes no extra pain compared to the standard biopsy techniques although it increases the number of biopsy cores and involves a relatively more complex procedure.

Table 1 - Clinical characteristics of the patients in both groups.

	Group I (n=159)	Group II (n=93)	p
Age (years)	61.82 (±7.39)	62.28 (±6.16)	0.612
Body mass index (BMI) (kg/m^2)	26.10 (22.80-27.70)	26.10 (22.80-28.30)	0.966
Total prostate volume (mm^3)	51.62 (34.00-71.73)	50.00 (40.00-60.00)	0.627
Serum PSA level (ng/dL)	6.99 (5.01-10.10)	8.01 (5.05-9.12)	0.615
Number of biopsy cores (n)	16.0 (15.0-19.0)	12.0 (11.0-12.0)	<0.001
Malignancy detection rate (n, %)	70/159 (44.0%)	24/93 (25.8%)	0.004

PSA = Prostate specific antigen

Table 2 - Comparison of pain levels in both groups.

	Group 1 (n=159)	Group 2 (n=93)	p
VAS score	2.0 (1.0-4.0)	3.0 (1.0-5.0)	0.070
Most painful step			0.140
Probe insertion	111/159 (69.8%)	58/93 (62.4%)	
Probe manipulation	22/159 (13.8%)	22/93 (23.6%)	
Needle piercing	26/159 (16.4%)	13/93 (14.0%)	

VAS = Visual analog scale

In a study conducted in 2018, Robins et al. reviewed 170 patients that underwent FPB or SPB and reported that no significant difference was found between the groups with regard to pain and discomfort (14). A previous prospective study by Arsoy et al. compared patient comfort between the patients that underwent MR-guided in-bore prostate biopsy and MRI/ultrasound fusion-guided prostate biopsy, in which PNB was induced by administering intrarectal anesthetic gel in all the patients, in a similar way to our study (15). The authors reported that FPB causes less pain compared to in-bore prostate biopsy although it increases the number of biopsy cores. In our study, the number of biopsy cores was higher in the FPB group compared to the SPB group. Despite the lack of supporting evidence, we consider that the acquisition of additional biopsy cores and the transfer of MpMRI images to the US fusion device are time-taking processes which lead to prolonged FPB procedures. However, despite these drawbacks of FPB, the pain levels experienced by the patients were revealed to be similar in both procedures.

Pain during transrectal prostate biopsy can be associated with the three steps of the biopsy procedure (i.e., insertion of the probe into the rectum, probe manipulation, and piercing of the biopsy needle) (16). In our study, we also divided the biopsy procedure into these three steps. Prior to the procedure, each patient was verbally informed about these steps and were asked to indicate the most painful step after the procedure. In both groups, the most painful step revealed to be the insertion of the probe into the rectum. A recent systematic review revealed that the administration of intrarectal anesthetic gel followed by PNB led to a lower degree of pain both during probe movements and needle piercing but had no remarkable effect on the pain experienced during the insertion of the probe (17). Urabe et al. compared the effectivity of intrarectal local anesthetic, PNB, and the combined methods in alleviating the pain during TRUS-guided SPB and reported that PNB led to lower pain levels during the insertion of the probe compared to other techniques (18). It should be noted that there are some studies in the literature which, in a similar way to our study, indicate that PNB alone or in combination with intrarectal gel leads to reduction in the pain experienced during probe manipulation and needle piercing (19, 20).

Literature reviews also indicate that there is a controversy in the literature as to whether the level of pain during biopsy can vary according to patient age and prostate volume (21-23). In our study, we found that the mean age and the median prostate volume were similar in both groups (p=0.612, p=0.627, respectively), which is important for implicating standardization and homogeneity.

A recent systematic review indicated that the overall cancer detection rate was 26.3%-56.6% in SPB as opposed to 33.7%-79.5% in FPB (10). Similarly, Fourcade et al. reported that the overall cancer detection rate was higher in FPB compared to SPB (45% vs. 33.5%, p=0.02) (24). In our study, we found that the malignancy detection rate was significantly higher in FPB compared to SPB (44% vs. 25.8%, p=0.004). We consider that this difference was expected since the SPB group only

comprised patients who were detected with a PI--RADS <3 lesion on MpMRI. On the other hand, it is also possible that the patients excluded from the study might have led to inconclusive or unrealistic results. Therefore, we consider that the oncological findings obtained in our study may not reflect the reality of the situation.

Our study was limited in several ways. First, our study had a relatively small patient population. Secondly, although the duration of FPB is known to be longer than that of SPB, we did not record the durations of the procedures and thus could not evaluate the association between the duration of the procedure and pain. Thirdly, we did not assess the VAS scores separately for each of the three steps of the procedure (probe insertion, probe manipulation, and needle piercing) and only asked the patients to indicate the most painful step after the procedure. As a result, we could not perform an objective evaluation on the biopsy steps. Finally, the location of the suspected lesion may be important for pain felt during the biopsy. In particular, sampling from the anterior region or central zone may cause more pain as it is more difficult to reach. Another limitation of this study was the lack of statistical comparison on subject of lesion localization/pain levels due to insufficient number of patients.

CONCLUSIONS

Despite that MRI-US fusion and taking additional cores prolonged the predicted duration of FPB which has higher cancer detection rate comparing with SPB, pain level during FPB was similar to SPB. We consider that these drawbacks of FPB do not have any adverse effects on pain. Further prospective studies with larger patient series are needed to substantiate our findings.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Comparison of pain levels in fusion prostate biopsy and standard TRUS-Guided biopsy

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COMMENT

It is overwhelming that the concern to diagnose better is being accompanied by diagnosing carefully. We see in this article the ultimate medical art that combines technological excellence and zeal with the well--being of our patients.

Following the tendency proposed by the English study PROMISS (1) authors applied the Multiparametric magnetic resonance imaging (MpMRI) in the screening scenario, using this tool for biopsy-naïve patients. Although they recognized a bias in the allocation of individuals, the evidence of a higher detection rate in the group with PIRADS ≥ 3 adds data to the literature and supports the indication of that refined imaging tool (2).

When fulfilling the objective of their study, the authors inform us about the similar pain potential of the technique under fusion of images in relation to the standard biopsy; demystifying one of the many questions about its use.

Despite all care taken by the team, their results reveal a major problem about the invasiveness of our procedures.

Let us remember the beginnings of the technique of image acquisition for MpMRI that included, pretty far behind, the use of endo-rectal coil (3). Certainly, in addition to being costly, impale (not to use more coarse terms) caused great discomfort to those who underwent that exam and diagnostic performance of MpMRI is not significantly different if endorectal coil is used or not (4). It didn't take long, the device is no longer part of the routine of radiology clinics, making it more acceptable to patients and recommended by urologists (5).

Prostate biopsy has long been stressful for all concerned.

Hematuria and hematochezia may cause fright and fear for the patient; but for his urologist, sepsis, prostatitis and acute urinary retention are source of great unease. Several studies have researched ways to reduce infectious complications (6) and literature proposes to understand how to turn the procedure safe and comfortable for the patient (7); and for the practitioner, faster and assertive, by improving skill acquisition techniques (8-11).

Various anesthetic approaches have been proposed and compared (12). Although the local anesthesia routes such as intrarectal local anesthesia (IRLA) and periprostatic nerve blockade (PNB) are the most common for the urologist (13), studies have assessed the suitability of total intra venous sedation (TIVS) (14). In a prospective randomized-controlled trial (RCT), Tobias-Machado et al. (15) demonstrated that application of PNB and TIVS together were associated to higher tolerance of the exam and patient comfort. In other study, authors provided TIVS alone and demonstrated a short procedure time with sufficient analgesia, allowing patients to be discharged less than 2 hours after biopsy (16).

In a recent meta-analysis study, one of its arms evaluated the employing of sedation for transrectal prostate biopsy; evidence suggests that TIVS and PNB allows a better approach (13). In Rio de Janeiro, Brazil, at the National Cancer Institute - INCa - a branch of the Department of Urology the Prostate Cancer Diagnosis Center - CDCP - routinely performs transrectal ultrasound guided biopsies of the prostate with the support of anesthetists who promote total intravenous sedation of properly monitored patients. Despite increasing the operational cost, the implementation of advanced anesthetic management makes the procedure safe and agile; by adopting the outpatient model, CDCP increased the availability of spaces for biopsies in state's public health system, with an installed capacity to perform 3600 procedures per year.

For most of the patients, several psychological factors, such as anxiety, make the procedure even more difficult (17, 18). Fear and embarrassment has been described as reasons for prostate biopsy refusal (19). Although the fear of pain seems obvious, it is necessary to discuss which pain the patient has the greatest aversion to. This study sheds light on this question and leads us to believe that not the needle, but the rectal introduction of a phallic object would be the main hassle factor to that individual already weakened by their cancer suspicion.

In daily urological practice, cultural aversion to digital rectal examination (DRE) is a precursor to a number of problems for the diagnosis of prostate cancer (20). We often hear from some patients the refusal to do the DRE and the exclusive acceptance of the PSA for their screening.

Paralleling the DRE, would our patients be more resentful of the offense to their masculinity caused by the ultrasound probe or does that pain really surpass that of the needle bites suffered? Qualitative studies, with adequate discourse analysis, could help us to understand this psycho-social aspect of our role (21).

In the present paper, our authors applied the most used anesthetic approach, IRLA and PNB, and highlights the absence of difference in pain pattern of both sample harvesting ways. In a study of similar comparison, but with quite different methods, another group of investigators have shown that men undergoing targeted and systematic prostate biopsies experience more discomfort and anxiety during the procedure than those undergoing systematic biopsy alone (17). The psychological factor was evaluated in both studies, suggesting the importance of this issue; in this sense, sedo-analgesia plays an important role when used together with local anesthesia (22, 23).

Regardless of the technique used, it is important to reduce the negative impacts that our invasive methods may cause on patients. After all, the waiting line is full and it is better that they say, "with this doctor, it didn't hurt at all".

CONFLICT OF INTEREST

None declared.

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The significance of preoperative estimated glomerular filtration rate on survival outcomes in patients who underwent radical cystectomy and non-continent urinary diversion

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ABSTRACT

Purpose: To evaluate the influence of preoperative renal function on survival outcomes in patients who underwent radical cystectomy (RC) with non-continent urinary diversion (UD).
Materials and Methods: A total of 132 patients with bladder cancer who underwent RC with non-continent UD due to urothelial carcinoma from January 2006 toMarch 2017 at our tertiary referral center were retrospectively evaluated. Patients were divided into 2 groups as those with estimated glomerular filtration rate (eGFR) <60mL/min/1.73 m2 and ≥60mL/min/1.73 m2 according to preoperative eGFR levels. Patients' characteristics, preoperative clinical data, operative data, pathologic data, oncologic data and complications were compared between the groups.
Results: The mean age was 64.5±8.7 (range: 32 - 83) years and the median follow-up was 30.9±31.7 (range: 1-113) months. There were 46 patients in Group 1 and 86 patients in Group 2. There was no difference in cancer-specific mortality (45.6% for group 1 and 30.2% for group 2, p=0.078) and survival (56.8±8.3 months for group 1 and 70.5±5.9 months for group 2, p=0.087) between the groups. Overall mortality was higher (63% for group 1 and 40.7% for group 2, p=0.014) and overall survival (43.6±6.9 months for group 1 and 62.2±5.8 months for group 2, p=0.03) was lower in Group 1 compared to Group 2.
Conclusions: Overall mortality was higher and overall survival was lower in patients with preoperative eGFR <60mL/s. More patients had preoperative hydronephrosis with eGFR< 60mL/s.

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INTRODUCTION

Radical cystectomy (RC) with extended pelvic lymph node dissection is the best choice of treatment in patients with non-metastatic muscle-invasive and high-risk non-muscle invasive bladder cancer (1-4). The procedure is completed with urinary diversion (UD) after the removal of the bladder. RC with UD is a 2-step, complex surgical procedure and is associated with significant risks of perioperative and long-term morbidity and mortality, including

renal function deterioration and development of chronic renal disease (CKD) (5, 6).

The etiology of a renal function decrease after RC is likely multifactorial, including age-related changes, potential nephrotoxic chemotherapy, and the impact of patient comorbidities, which are frequent in such a population, and postoperative urinary tract obstruction and infection-related complications (7). Renal dysfunction is fairly common in this group of patients. Patients with bladder cancer largely comprise middle aged and elderly people (8). This is indicative of the presence of many morbidities that accompany bladder cancer in patients. Hamano et al. found that advanced preoperative CKD stage was significantly associated with poor oncological outcomes of bladder cancer after RC (8).

Comorbidities such as hypertension (HT), diabetes mellitus (DM) and vascular disease are important risk factors for the development of CKD at advanced age (9). Matsumoto et al. discussed the precise biological mechanism of association between tumor aggressiveness and CKD status with possible explanations. They found chronic inflammation induced by continuous exposure to oxidative stress and accompanying immune deficiency to be responsible mechanisms for CKD (10).

An important point in the evaluation of renal dysfunction is the method of choice to calculate the renal function. Most studies evaluate renal function variations using serum Δ creatinine as a surrogate value for the estimated glomerular filtration rate (eGFR) (11). Makino et al. assessed eGFR alterations over the years and risk factors for decreasing eGFR. Deterioration in renal function in early and late postoperative years was defined as a ≥25% decrease in the eGFR from preoperative to postoperative year one and a reduction in the eGFR of >1mL/min/1.73m2 annually in subsequent years (12).

In this study, we aimed to evaluate the influence of preoperative renal function on oncological outcomes and prognosis in patients who underwent RC and non-continent UD.

MATERIALS AND METHODS

A total of 132 patients with bladder cancer who underwent RC with non-continent UD due to urothelial carcinoma from January 2006 to March 2017 at our tertiary referral center were retrospectively evaluated. Patients were divided into 2 groups as eGFR <60mL/s and ≥60mL/s according to preoperative eGFR levels. Patients without urothelial carcinoma on pathological examination, presence of upper tract urothelial carcinoma or obstructive stones and patients with incomplete medical records were excluded from the study. Patient characteristics, preoperative, operative and follow-up data were reviewed. The indications for RC were tumor invasion into the muscularis propria or prostatic stroma, or non-muscle-invasive disease (Ta, T1, or carcinoma in situ) refractory to transurethral resection with intravesical therapy.

Patient's characteristics (age, gender, presence of DM, HT and other comorbidities), preoperative clinical data (preoperative and postoperative at 3 months and creatinine and eGFR levels, American Society of Anesthesiologists (ASA) score, Eastern Cooperative Oncology Group (ECOG) performance score, Charlson comorbidity index and hydronephrosis presence, grade and laterality), operative data (operation time and diversion type data), pathologic data (preoperative T stage, tumor grade and carcinoma in situ (CIS) presence, postoperative T stage and tumor grade, surgical margin positivity, number of dissected lymph nodes, positive lymph node ratio, lymph node metastasis and percentage of positive lymph node data), oncologic data (upstaging, adjuvant chemotherapy, overall mortality (OM) and overall survival (OS), cancer specific mortality (CSM) and CSS and complications (hospitalization time, early medical complication, early surgical complications, complication data of Clavien-Dindo classification) were evaluated.

Type of incontinent urinary diversions were ureterocutaneostomy and incontinent ileal conduit. Creatinine was defined as difference between postoperative 3rd month creatinine and preoperative creatinine. Hydronephrosis was defined by anteroposterior diameter of the renal pelvis >10mm which was diagnosed by renal ultrasound or CT scan with or without secondary changes of renal parenchyma or renal function.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, Ill) software program. According to preoperative eGFR levels, patients were divided into two groups as preoperative eGFR <60mL/s (Group 1) and preoperative eGFR ≥60mL/s (Group 2) groups. Mann-Whitney U test and Pearson Chi-square test analyses for univariate analysis and binary logistic regression analysis for multivariate analysis were used between the groups. In addition, Kaplan-Maier survival analysis and the log-rank test were used for OS and CSS times between groups. In addition, same tests were used for univariate and multivariate analysis of the factors affecting on overall and cancer specific deaths. A Cox regression model was created for evaluating the predictive factors on overall survivals. Data are given as mean±SD. However, results of analysis are given as median data. Statistical significance was defined as $p < 0.05$.

RESULTS

Patients characteristics

The mean age was 64.5±8.7 (range: 32-83) years and the median follow-up time was 30.9±31.7 (range: 1-113) months. Consistent with previous data, there was a limited number of female patients (12 of 132, 9%). Mean OS and CSS of all patients were 56.3±4.7 and 67.1±5 months, respectively. There were 46 patients in Group 1 and 86 patients in Group 2. Comparison of patient's characteristics and preoperative clinical data between Group 1 and Group 2 according to preoperative eGFR levels were given in Table-1. In univariate analysis, the distributions of HT, DM, comorbidity data, ASA score, ECOG performance score and Charlson comorbidity index were similar, only preoperative hydronephrosis presence and hydronephrosis laterality were found to be significantly higher in Group 1 compared to Group 2. Preoperative and postoperative creatinine and eGFR at the third month and creatinine levels of the groups are given in Table-1 to show mean creatinine and eGFR data. When we evaluated the peroperative and postoperative results and pathologic data between the groups, any prognostic and pathologic data were significant.

Oncological outcomes

Mean OS and CSS of all patients were 56.3±4.7 and 67.1±5 months, respectively. Overall and cancer specific deaths were 64 and 47 in all patients. In the comparison of oncological outcomes, although there was no difference in cancer specific mortality (45.6% for group 1 and 30.2% for group 2, p=0.078) and CSS (56.8±8.3 months for group 1 and 70.5±5.9 months for group 2, p=0.087) between the groups, OM was higher (63% for group 1 and 40.7% for group 2, p=0.014) and OS (43.6±6.9 months for group 1 and 62.2±5.8 months for group 2, p=0.03) was lower in Group 1 compared to Group 2. Survival plots are given in Figure-1. Furthermore, upstaging and adjuvant chemotherapy rates were similar between the groups. Oncological data and survival findings are given in Table-2 and Table-3. Also, univariate and multivariate analysis results of the factors affecting on overall and cancer specific deaths are given in Table-4. Preoperative eGFR was significantly associated with overall death. In addition, preoperative eGFR (p=0.041, OR:0.514, CI:1.022-2.738), preoperative hydronephrosis (p=0.002, OR:0.878, CI:0.240-0.721), age (p=0.038, OR:0.03, CI:1.002-1.061) and pathological T stage (p=0.013, OR:0.349, CI:0.136-0.619) were found to be associated with overall survival after radical cystectomy in Cox regression model (p=0.001). In groups, hospitalization time, early medical and surgical complication rates, and complication rates according to Clavien-Dindo classification were also similar.

DISCUSSION

There is ongoing debate about the effect of preoperative patient status on the surgical outcomes after radical cystectomy. CKD, HT, DM and vascular diseases are well-known risk factors which have negative impact on surgical outcomes. An independent, graded association was observed between reduced eGFR and the risk of death, in a large, community-based population. These findings highlight the clinical and public health

Table 1 - Comparison of patient's characteristics and preoperative findings between eGFR <60mL/min/1.73m2 and eGFR ≥60mL/min/1.73m2 groups according to preoperative eGFR levels.

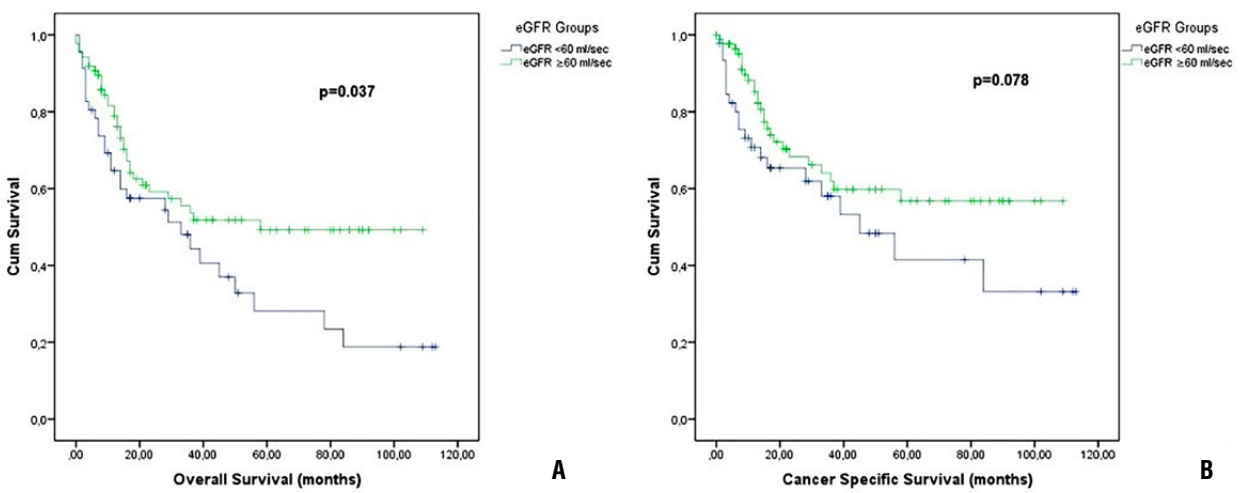
		Preoperative eGFR <60mL/min/1.73m2 (n=46)	Preoperative eGFR ≥60mL/min/1.73m2 (n=86)	p
Age (years) (mean±SD)		65.9±9.5	63.7±8.2	0.145
Gender	Female	7	5	0.073
	Male	39	81	
Preoperative creatinine (mean±SD)		1.69±0.57	0.96±0.15	-
Preoperative eGFR (mean±SD)		41.6±13	80±16.9	-
Postoperative 3 month creatinine (mean±SD)		1.72±0.66	1.21±0.57	<0.001
Postoperative 3 month eGFR (mean±SD)		45±18.4	69.9±22.9	<0.001
Δ creatinine (mean±SD)		0.04±0.66	0.26±0.55	0.015
ASA	1	1	4	0.218
	2	3	46	
	3	12	34	
	4	0	2	
ECOG Performance score	0	8	25	0.364
	1	24	36	
	2	9	16	
	3	3	7	
	4	1	0	
Charlson comorbidity index	0	0	1	0.295
	1	1	2	
	2	13	13	
	3+	32	70	
DM, n (%)		10 (21.7)	15 (17.4)	0.548
HT, n (%)		24 (52.2)	30 (34.9)	0.054
Any comorbidity, n (%)		37 (80.4)	60 (69.8)	0.186
Preoperative hydronephrosis	positive	30	23	<0.001
	negative	16	63	*<0.001
Hydronephrosis laterality	unilateral	18	21	0.01
	bilateral	12	2	*0.019
Preoperative hydrophrosis grade	1	1	4	0.276
	2	9	4	
	3	15	10	
	4	5	5	
Preoperative nephrostomy tube insertion for grade 3-4 hydrophrosis		12 (60)	7 (46.7)	0.767

Mann Whitney U test and Pearson Chi-square test.

*Binary logistic regression analysis for significant data of univariate analysis results.

ASA = American Society of Anesthesiologists; **ECOG** = Eastern Cooperative Oncology Group; **DM** = Diabetes mellitus; **HT** = Hypertension

Figure 1 - A) Overall survival plots of Kaplan-Maier analysis. B) Cancer specific survival plots of Kaplan-Maier analysis.



importance of chronic renal insufficiency (13). Interest in the influence of preoperative renal insufficiency on cancer prognosis has increased because of its prevalence in elderly patients with muscle-invasive bladder cancer (3). Eisenberg et al. reported that decreased renal function is noted in most patients during long--term follow-up after radical cystectomy and approximately 70% of patients undergoing RC with UD experience eGFR decline postoperatively. They also stated that choice of urinary diversion was not independently associated with decreased renal function (7).

Despite the variety of diversion techniques, either continent or non-continent, patients undergoing RC have a life-long risk of CKD (11). Continent diversion methods are mostly not preferred in the case of preoperative CKD, while de Toledo et al. emphasized that gastric neobladder can be used in highly selected cases (e.g., renal insufficiency) because of its high morbidity and mortality rates (14). According to the selected diversion method, our study group consisted of patients with non--continent diversion. There were 77 patients with ileal conduit diversion (ICD) and 55 patients with ureterocutaneostomy (UC). Our patients were divided into 2 groups to compare the effect of preoperative eGFR on oncologic results. In patients with preoperative eGFR <60mL/s, preoperative creatinine level increased from 1.69±0.57 to 1.72±0.66. However, creatinine levels were worse in patients with preoperative eGFR ≥60mL/s (increased from 0.96±0.15 to 1.21±0.579). This situation can be explained as relative improvement due to the regression of preoperative hydronephrosis in patients with preoperative eGFR <60mL/s. In the comparison of groups, more patients already had preoperative hydronephrosis in Group 1. Urinary tract obstruction was the leading cause of long-term renal function impairment, regardless of whether the patient had ileal conduit diversion or orthotopic ileal bladder substitution. Also, Eisenberg et al. reported that age, preoperative kidney function and chronic hypertension, and the postoperative complications of hydronephrosis, pyelonephritis and uretero-enteric anastomotic stricture were associated with an increased risk of decreased renal function (7). Our findings support the effect of preoperative hydronephrosis on renal functions and oncologic outcomes.

In recent years, population-based studies reported a slow increase in cancer risk as CKD status progressed (15, 16). In a previous study, it was found that patients with CKD had worse prognosis, higher tumor recurrence and progression rates in primary non-muscle invasive bladder cancer (17). In some other stu-

Table 2 - Comparison of operative and pathologic data between Group 1 and Group 2.

		Preoperative eGFR <60mL/min/1.73 m2 (n=46)	Preoperative eGFR ≥60mL/min/1.73 m2 (n=86)	P*
Preoperative T stage	≤T1	6	9	0.721
	T2	38	75	
	T3	2	2	
Preoperative tumor grade	Grade1	1	2	0.485
	Grade2	3	2	
	Grade3	42	82	
CIS	positive	10	30	0.108
	negative	36	55	
Operation time (hours)		5.6±1.3	5.8±1.1	0.369
Postoperative T stage	T1	8	20	0.364
	T2	17	39	
	T3	8	13	
	T4	13	14	
Postoperative tumor Grade	1	3	5	0.905
	2	1	3	
	3	37	68	
Surgical margin positivity	positive	13	13	0.07
	negative	33	73	
Number of dissected lymph node		12.4±5.9	13.2±4.9	0.430
Positive lymph node ratio		1.1±2.4	0.4±1.2	0.121
Lymph node metastasis	Positive	11	14	0.318
	Negative	34	68	
Percentage of positive lymph node		8.9±19.1	3.5±9.4	0.136
Diversion type	Ureterocutaneostomy	23	32	0.156
	Ileal conduit	23	54	

*Mann Whitney U test and Pearson Chi-square test
CIS = Carcinoma In Situ

dies, it was shown that poor oncologic results accompany CKD in muscle-invasive bladder cancer patients who underwent RC (18, 19). There is an age-dependent physiological decrease in eGFR, which was defined as a >10mL/min/1.73m2 drop in eGFR from baseline, which occurs per decade (20). In the current study, overall mortality and survival were significantly worse with preoperative eGFR <60mL/s. CKD might not only limit long-term outcomes by increasing the risk of cardiovascular morbidity and mortality, but also compromise short--term outcomes (13).

Long-term renal function after RC can be adversely affected by several factors, including age, potential nephrotoxic chemotherapy, comorbidities, and diversion-related factors (11). Physicians dealing with uro-oncology

mostly prefer non-continent diversion techniques instead of orthotopic neo-bladder formation in patients with concomitant morbidities such as CKD, cardiovascular or advanced chronic obstructive lung disease.

We showed that overall survival and mortality were poorly affected by low eGFR in patients undergoing non-continent diversion. Our study was limited by its retrospective design and small number of patients. Also, the threshold value to define renal failure is heterogeneous in different studies. Blood urea and creatinine estimations are easy and inexpensive, but these biochemical parameters can

Table 3 - Comparison of postoperative data, complications and survival findings between Group 1 and Group 2.

		Preoperative eGFR <60mL/min/1.73 m2 (n=46)	Preoperative eGFR ≥60mL/min/1.73 m2 (n=86)	p
Upstaging	Positive	22	55	0.073
	Negative	24	31	
Upstaging	upstaging	24	31	0.160
	downstaging	5	17	
	No differance	17	38	
Adjuvant chemotherapy, n (%)		12 (26.1)	22 (25.6)	0.950
Overall Mortality, n (%)		29 (63)	35 (40.7)	0.014
				*0.015
Overall Survival		43.6±6.9	62.2±5.8	#0.037
Cancer Specific Mortality, n (%)		21 (45.6)	26 (30.2)	0.078
Cancer Specific Survival		56.8±8.3	70.5±5.9	#0.087
Surgery time (hours)		5.6±1.3	5.8±1.1	0.518
Hospitalization time		11.3±4.6	12.1±6.3	0.475
Early medical complication	Positive	14	20	0.369
	Negative	31	66	
Early surgical complication	Positive	15	41	0.095
	Negative	31	45	
Clavien-Dindo	1	5	8	0.357
	2	34	51	
	3a	1	2	
	3b	3	15	
	4a	1	7	
	5	2	3	

Mann Whitney U test and Pearson Chi-square test
*Binary logistic regression analysis for significant data of univariate analysis results
Kaplan-Maier survival analysis and the log-rank test

Table 4 - Univariate and multivariate analysis of the factors affecting on overall and cancer specific death.

		Overall death			Cancer specific death		
		n=64	p	p*	n=47	p	p*
Preoperative hydronephrosis	Positive	35	0.001	0.071	27	0.002	0.052
	Negative	29			20		
Preoperative T stage	≤T1	8	0.501	-	5	0.247	-
	T2	53			39		
	T3	3			3		
eGFR (mL/sec)	<60	29	0.014	p=0.040	21	0.078	-
	≥60	35		HR:2.33 (CI:1.04-5.22)	26		
Postoperative T stage	T1	10	<0.001	0.118	6	<0.001	0.614
	T2	19			13		
	T3	13			10		
	T4	22			18		
Postoperative tumor Grade	1	4	0.988	-	3	0.890	-
	2	2			2		
	3	55			40		
Surgical margin positivity	Positive	22	<0.001	0.087	19	<0.001	0.109
	Negative	42			28		
Lymph node metastasis	Positive	17	0.016	0.284	15	0.003	0.076
	Negative	42			28		
Upstaging	Positive	36	0.001	0.544	29	0.001	0.467
	Negative	28			18		

*Multivariate analysis results

be affected by different metabolic events. In fact, each diversion method leads to subtle metabolic changes causing confused results. As far as finding the ideal method, eGFR seems to give best results for the measurement of renal failure.

CONCLUSIONS

Preoperative hydronephrosis, which is a well-known prognostic factor in patients undergoing radical cystectomy, was significantly higher in patients with eGFR <60mL/s. Overall mortality was higher and overall survival was lower in patients with preoperative eGFR <60mL/s. Renal dysfunction is an important risk factor for overall survival in patients who undergo radical cystectomy.

CONFLICT OF INTEREST

None declared.

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The relation between the storage symptoms before and after transurethral resection of the prostate, analysis of the risk factors and the prevention of the symptoms with solifenacin

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ABSTRACT

Objective and Hypothesis: We aimed to investigate the reasons of storage symptoms (SS) after transurethral resection of the prostate (TURP). The hypothesis was that a positive correlation would be identified between preoperative and postoperative SS in patients with undergoing TURP and starting early solifenacin treatment in patients with high preoperative SS would be reasonable. In addition, we aimed to analyze multiple other risk factors for post-TURP SS.

Materials and Methods: A total of 160 patients undergoing TURP were prospectively evaluated and divided into two groups according to their OABS. Those with a score of ≥10 points were Group 1 (G1), and those with <10 points Group 2 (G2). In addition, patients in each group were randomly further divided into two subgroups: those who were started on 5 mg solifenacin succinate in the early postoperative period (G1/G2 A) and those who were not (G1/G2 B). In additions to SS Preop, perop and at the 3rd-month of postoperatively 14 variable were evaluated. The effects of these factors, surgery and the efficacy of an early medical treatment on the postoperative SS were investigated. LUTS were assessed by International Prostate Symptom Score (IPSS) and SS were assessed by sum of IPSS 2, 4 and 7 questionnaires (Storage, S- IPSS).

Results: Preoperative IPSS and S-IPSS were significantly higher in G1 ($p<0.001$); there was a significant improvement at IPSS, S-IPSS, QoL score, Qmax, and PVR for all groups after surgery. Only preoperative S-IPSS was found to have significant effect on postoperative SS ($p<0.001$). There was a significant difference between G1A and G1B but no significant difference between G2A and G2B in terms of SS at postoperatively. In addition to this, prostatic volume was found smaller than non-symptomatic patients in de novo SS patients.

Conclusion: TURP provides significant improvement in both storage and voiding symptoms. The predictive value of the preoperative S-IPSS on postop SS is significant. These results suggest that 5 mg solifenacin succinate treatment in the early postoperative period may be beneficial for patients with high preoperative SS and may not be beneficial in others. Small prostatic volume may bode ill for postoperative SS in the patients with de novo SS.

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INTRODUCTION

Transurethral resection of the prostate (TURP) is the most effective surgical treatment option for benign prostatic hyperplasia (BPH) and is still the gold standard and it has been shown to provide significant, sustained decrease in lower urinary tract symptoms (LUTS) and improvements in urodynamic parameters (1). However, voiding and storage symptoms (SS) during the postoperative period negatively affect quality of life (2). It has been reported that overactive bladder symptoms (OABS) persist in 20-35% of cases after TURP (3).

It is important for the surgeon and patients to know which group of patients is under risk for development of OABS after TURP. Several studies have shown that the success rates in the postoperative period were lower in patients with preoperative urodynamic detrusor overactivity (DO) and preoperative severe SS, although the data on this subject are contradictory (4-11). So there is no consensus in this issue, which therefore needs further studies.

Therefore, we conducted this prospective randomized study. We aimed to investigate the reasons of SS after transurethral resection of the prostate (TURP). The hypothesis was that a positive correlation would be identified between preoperative and postoperative SS in TURP and starting early solifenacin treatment in patients with severe preoperative SS would be reasonable. In addition, we aimed to analyze multiple other risk factors such as age, PSA, prostatic volume, energy sources, resection time, duration of postoperative catheterization, pathology results etc. for post-TURP SS including de-novo SS and nocturia.

MATERIALS AND METHODS

Patients

A total of 204 patients presented to our hospital between January 2014 and March 2017 who were candidates for TURP were enrolled. Following the approval of the study required local Ethics Committee (Issue: 42232755-799-E.54), patients were informed about the study and written consent forms were obtained.

Patients with moderate to severe symptom scores were included in the study. A total of 44 patients were excluded from the final analyses because they had a history of urologic surgery, prostate or bladder cancer pathology, bladder stone, suspected neurogenic disease, urinary retention, or ongoing anticholinergic medication preoperatively, and patients with urinary infection (n=5), urethral stricture formation (n=7), positive pathology results for cancer (n=3), clot retention on postoperative period (n=3), those who could not tolerate medical treatment (n=2) during the postoperative period and the those who missed the follow-up visits (n=6). After exclusion, the analysis was completed with remaining 160 patients.

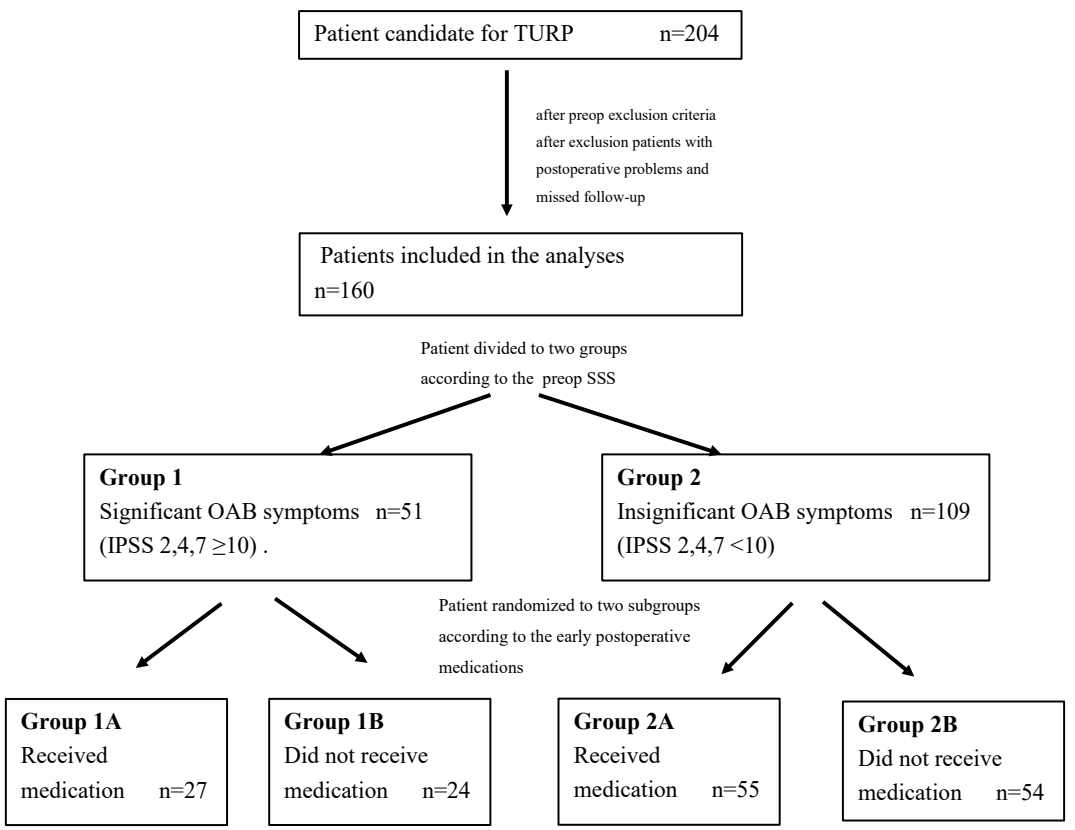
Patient's LUTS were assessed by International Prostate Symptom Score (IPSS) and SS scores were assessed by total scores of İPSS 2, 4 and 7 questionnaires (S-IPSS) because IPSS was validated in many languages around the World, safely used in previous studies, and its use is more convenient. Patients were divided into two groups according to their preoperative S-IPSS scores: those with significant SS scores (S-IPSS >10) in the preoperative period (G1) and those not (G2). Before the operation, patients in each group were randomly assigned to two subgroups according to their received medication: those who received medication in the postoperative period (G1A or G2A) and those did not (G1B or G2B). Solifenacin treatment was started after operation before discharge from the hospital. The workflow diagram is shown in Figure-1.

Patients with a score of <8 points in the postoperative assessment or a reduction of more than 50% in S-IPSS (compared to their preoperative score) were considered as improvement.

In addition to S-IPSS, 17 other variables were analyzed (Table-1). Surgery was performed using a 26Fr monopolar resectoscope (Karl Storz, Germany) and a 26Fr plasma kinetic bipolar resectoscope (Gyrus Agmi, US). The starting and finishing times of the resection were recorded. The choice of energy source was determined randomly at the intraoperative period. Solifenacin 5mg once daily was prescribed as postoperative medications in the study group before discharge from the hospital.

Figure 1 - Study flow scheme

A total of 204 patients candidate to TURP were enrolled the study. After exclusion, 160 patients completed 3 months follow-up study and the results were analyzed. Patients were divided two groups according to the preoperative SS severity. Those with a S-İPSS score of ≥10 points were included in Group 1 (G1), and those with <10 points in Group 2 (G2). In addition, patients in each group were randomly further divided into two subgroups: those who were started on 5mg solifenacin succinate in the early postoperative period (G1/G2 A) and those who were not (G1/G2 B).



TURP = Transurethral prostatectomy; **IPSS** = İnternational prostate symptom scores; **SS** = storage symptoms.

The questionnaires were re-implemented at postoperative 3rd-month visit, pathology results were evaluated, and uroflowmetry and PVR were assessed.

Statistical analysis

Mann-Whitney U test was used to compare two independent variables not fitting to normal distribution. The Wilcoxon test was used to compare two dependent variables not fitting to normal distribution between two groups. The Kruskal-Wallis test was used to compare the independent continuous variables not fitting to normal distributions between more than two groups. The $\chi 2$ test (or the Fisher Exact test where appropriate) was used to compare categorical variables between study groups. Statistical significance level was accepted as $p<0.05$. Analyses were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software BVBA, Ostend, Belgium; http://www.medcalc.org; 2013).

RESULTS

Preoperative and perioperative findings

Data for the preoperative and perioperative period are presented in Table-1. No significant difference was found between groups in terms

Table 1 - Preoperative and perioperative data for the patient groups.

Characteristic	All	Group 1A	Group 1B	Group 2A	Group 2B	p
Age (year)	65.4 ± 7.8	67.3 ± 8.9	63.9 ± 5.3	65 ± 8.5	65.7 ± 7.6	0.328*
PSA (ng/mL)	2.59 ± 3	3.7 ± 5	2.8 ± 3.6	2.1 ± 1.4	2.4 ± 2.5	0.548*
Prostate Size† (gr)	54.1 ± 12	50.8 ± 17.8	47.2 ± 15.6	57.6 ± 16.9	55.2 ± 14.1	**0.047***
Preoperative Parameters						
IPSS	24.8 ± 5.8	28.7 ± 6.3	27.2 ± 6.5	23 ± 4.9	23.8 ± 5.2	**<0.001**
S-İPSS	7.4 ± 3.8	11.3 ± 1.9	12.5 ± 1.7	5.4 ± 2.6	5.2 ± 2.4	**<0.001**
QoL	5.19 ± 0.6	5.3 ± 0.6	5.2 ± 0.7	5.2 ± 0.7	5.1 ± 0.6	0.502
Qmax (mL/sn)	7 ± 3.3	7.9 ± 3.4	8.1 ± 3.2	6.4 ± 3.2	6.8 ± 3.4	0.097
PVR (mL)	61.8 ± 24	47.9 ± 15.7	49.04 ± 9.3	68.2 ± 23.3	68.2 ± 29.4	**<0.001**
Resection Time, min	45.5 ± 12.3	44.5 ± 15	44.3 ± 14.1	46.4 ± 10.6	45.8 ± 12.1	0.263*
Postop Cat (day)	3.8 ± 0.9	3.9 ± 0.9	3.8 ± 0.9	3.9 ± 0.9	3.7 ± 0.9	0.491*
Pathology Result, n (%)						
BPH		15 (55.6)	12 (50.0)	26 (47.3)	24 (44.4)	0.823**
BPH, Prostatitis		12 (44.4)	12 (50.0)	29 (52.7)	30 (55.6)	
Energy Source, n (%)						
Bipolar		11 (40.7)	9 (37.5)	20 (36.4)	20 (37)	0.990**
Monopolar		16 (59.3)	15 (62.5)	35 (63.6)	34 (63)	

post hoc paired comparison	**Group 1 a vs. 1 b**	**Group 1 a vs. 2 a**	**Group 1 a vs. 2 b**	**Group 1 b vs. 2 a**	**Group 1 b vs. 2 b**	**Group 2 a vs. 2 b**
Prostate size	0.521	0.088	0.184	0.013	0.034	0.645 ***

Continuous variables are expressed as mean ± SD

* = Kruskal-Wallis test; ** = Fisher's Exact test; *** = Mann-Whitney U p

PSA = Prostate specific antigen; I**PSS** = International prostate symptom score; **QoL** = Quality of life, **Qmax:** Maximum flow rate; **PMR** = Postvoid residual urine; Postop Cat = Duration of postoperative catheterization; **BPH** = Benign prostate hyperplasia; **SD** = standard deviation.

† = Patients in Group 1B has significantly lower prostate size compared to Groups 2A and 2B (p=0.013 and p=0.034, respectively).

of age and preoperative PSA. The mean prostate volume was 50.5±15.1g in the study population. There was a significant difference between groups in terms of prostate volume (p=0.047) in multi-group comparison. Patients in Group 1B has significantly lower prostate size compared to Groups 2A and 2B (p=0.013 and p=0.034, respectively). However, no significant difference was found in

paired group comparisons between Groups 1B-2A and 1B-2B (p=0.013 and p=0.034, respectively (post hoc paired comparison). No significant difference was found between the groups in terms of perioperative resection time, energy source, prostate tissue pathology results and postoperative catheterization times (Kruskal-Wallis test, Fisher's Exact test, Mann-Whitney U test p >0.008, with Bonferroni correction). No difference in Qmax and QoL scores values were found between the groups in the preoperative period. The mean preoperative PVR was 61.8±24.7mL. Preoperative PVR in Group 2 was found significantly higher than Group 1 (p<0.001). The mean preoperative IPSS and S-IPSS scores were 26.1±4.7 and 7.4±5.8 in all patients, respectively. These were found significantly higher in Group 1 than Group 2 (p <0.001).

Postoperative results

One hundred and sixty patients after the exclusion criteria were analyzed. Data for the postoperative period are shown in Table-2. In all patients, the mean IPSS and S-IPSS scores were 8.14±6.9 points and 5.1±3.8 points at postoperative 3rd month, respectively. In all groups, significant improvements were found in the IPSS scores from the preoperative period to postoperative 3rd month (p <0.001). In the comparison of preoperative and postoperative S-IPSS scores, which represent the irritative symptoms, a significant improvement was found between Group 1A, 1B, and 2A (p<0.008) but not in Group 2B (p=0.126). The mean Qmax at postoperative 3rd month was 22.5±6.9. In all groups, significant improvements were found in Qmax (p<0.001). Postoperative QoL score was 2±1.2 in all patients. In all groups, significant improvements were found in QoL (p<0.001). The mean PVR at postoperative 3rd month was 22.4±16.4mL in all patients. Postoperative PVR was found significantly higher in Group 2 compared with Group 1. In the analysis of the effect of medical treatment on postoperative PVR, no difference was found between Groups A and B in post hoc paired comparison.

Overview of storage symptoms

The mean postoperative 3rd-month S--IPSS score in all patients was 5.1±3.8; the number of patients with a score of pre-operative ≥8 points decreased from 74 to 36 in the postoperative period, equivalent to a 48.6% improvement. The mean S-IPSS scores were 5.1±2 in Group 1A, 7.6±2.6 in Group 1B, 4.6±4.9 in Group 2A, and 4.5±3.6 in Group 2B. Group 1B was found to be significantly different than other groups in terms of the improvement in storage symptoms. The proportions of patients with a 50% or more reduction in symptom score were 74.1% in Group 1A, 29% in Group 1B (p <0.01), 49% in Group 2A, and 42% in Group 2B (p=0.52). The proportion of patients with postoperative S-IPSS scores of <8 points were 96.3% in Group 1A, 54.2% in Group 1B, 74.5% in Group 2A, and 81.5% in Group 2B, significant improvements were found in all groups except for Group 1B (p <0.001). In Group 2, in which patients had low rate of preoperative SS, the rate of those with symptom scores of ≥8 points was 22% (n=24) in the postoperative period. This rate represents de novo effect of TURP on the storage symptoms (SS).

Analysis of the factors that may be effective on SS

The preoperative factors that may be effective on postoperative SS were analyzed by a multiple linear regression model, and the preoperative S-IPSS score was found to have significant effect (p<0.001). One-unit increase in the preoperative S-IPSS score increases postoperative S-IPSS score by 0.609 points. In addition to the regression analysis, there was a significant, moderate positive correlation (Spearman's rho p<0.001) between the postoperative and preoperative S-IPSS scores. All other variables including age, PSA, prostate size, duration of resection, pathology results, energy source, and catheter duration were found to have no effect on the outcome (p>0.05 for all).

The analyses of nocturia and de novo SS

The results of the nocturia analyses (IPSS-7) show that its scores significantly decreased after operations in all groups (p <0.001). There is a significant difference between G1 and G2 patients at the preoperative and postoperative period (p <0.001). Pairwise comparison of the groups shows that there is a significant difference between

Table 2 - Changes in the values of parameters from preoperative to postoperative 3rd months.

Variable	All	Group 1A	Group 1B	Group 2A	Group 2B	p*	Post-hoc comparisons***		
								Preop	*Postop*
IPSS Preop	24.8 ± 5.8	28.7 ± 6.3	27.2 ± 6.5	23.05 ± 4.9	23.8 ± 5.2	**<0.001**	Group 1A vs Group1B	0.399	**0.005**
Postop 3-m	8.14 ± 6.9	6.5 ± 2.3	12.2 ± 9.3	8.4 ± 8.4	7 ± 4.7	0.064	Group 1A vs Group 2A	**<0.001**	0.847
p**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**		Group 1A vs Group 2B	**<0.001**	0.972
							Group 1B vs Group 2A	**0.001**	0.038
							Group 1B vs Group 2B	**0.005**	0.018
							Group 2A vs Group 2B	0.179	0.995
IPSS247 Preop	8.14 ± 6.9	11.3 ± 1.9	12.5 ± 1.7	5.4 ± 2.6	5.2 ± 2.4	**<0.001**	Group 1A vs Group1B	0.022	**<0.001**
Postop 3-m	5.1 ± 3.8	5.1 ± 2	7.6 ± 2.6	4.6 ± 4.9	4.5 ± 3.6	**0.001**	Group 1A vs Group 2A	**<0.001**	0.159
p**	**<0.001**	**<0.001**	**<0.001**	**0.034**	0.126		Group 1A vs Group 2B	**<0.001**	0.242
							Group 1B vs Group 2A	**<0.001**	**0.003**
							Group 1B vs Group 2B	**<0.001**	**<0.001**
							Group 2A vs Group 2B	0.652	0.522
QoL Preop	5.19 ± 0.6	5.3 ± 0.6	5.2 ± 0.7	5.2 ± 0.7	5.1 ± 0.6	0.502			
Postop 3-m	2.0 ± 1.2	2.1 ± 1.3	2.5 ± 1.2	2.04 ± 1.5	2.1 ± 1.2	0.547			
p**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**				
Qmax Preop	7 ± 3.3	7.9 ± 3.4	8.1 ± 3.2	6.4 ± 3.2	6.8 ± 3.4	0.097			
Postop 3-m	22.5 ± 6.9	21.9 ± 7.1	25.2 ± 6.5	23.9 ± 5.5	22.1 ± 6.8	0.072			
p**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**				
PVR Preop	61.8 ± 24	47.9 ± 15.7	49.04 ± 9.3	68.2 ± 23.3	68.2 ± 29.4	**<0.001**	Group 1A vs Group1B	0.940	0.061
Postop 3-m	22.4 ± 16.4	23.8 ± 16.6	14.3 ± 13.2	26.7 ± 17.1	20.9 ± 15.9	**0.003**	Group 1A vs Group 2A	**<0.001**	0.096
p**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**		Group 1A vs Group 2B	**0.001**	0.956
							Group 1B vs Group 2A	**<0.001**	**<0.001**
							Group 1B vs Group 2B	**0.001**	0.038
							Group 2A vs Group 2B	0.516	0.028

***** = Kruskal-Wallis test; ****** = Wilcoxon test ; ******* = Mann-Whitney U test

IPSS: International prostate symptom score, **QoL**: Quality of life, Qmax: Maximum flow rate, **PVR**: Post-void residual urine.

group 1A and group 1B at the postoperative period (p=0.024) whereas there is no difference between group 2A and 2B (p=0.251).

De novo OABS was defined by a rising of storage symptoms after operations. Patients with mild preoperative SS (S-IPSS is lower than 8 points) and severe postoperative SS (S-IPSS is higher than 10 points) were considered have de novo SS. In this respect, only the patients in group 2 were evaluated because these patients did not have significant SS preoperatively. The analyses showed that 22% of all patients have experienced de novo SS (35 of the 160). The comparisons between the subgroups showed that there were significant differences in terms of preoperative S--IPSS scores (<0.001), preoperative Q max values (mL/sec) (p<0.001) and prostatic volumes (mL) (p<0.003).

DISCUSSION

Transurethral resection of the prostate (TURP) is still the gold standard surgical treatment option for relief storage and voiding symptoms related to BPH and cause significant, sustained decrease in lower urinary tract symptoms (LUTS) including nocturia and improvements in urodynamic parameters (1).

Similarly, in our study the improvement of İPSS, S-IPSS, İPSS-7, QOL, PVR and Q max were statistically significant(p<0.001) All of these results are consistent with previous studies and demonstrate the effectiveness of traditional TURP in treating the symptoms of BPH.

Re-innervation of the bladder and restoration of detrusor stability as a result of the elimination of the obstruction and decreases of PVR were suggested as an effective factor to explain the reasons for the improvement in storage symptoms after TURP (12, 13). But in contrast to voiding symptoms, the storage symptoms do not clearly correlate with BOO, and may also occur independently of BOO. For this reason, OAB symptoms may persist after pharmacological and surgical treatment of BOO (14, 15).

In a study by De Nunzio et al., DO was shown to decrease from 68% to 31% within 2 years after prostatectomy (54% regression) (15). In our study, the rate of improvement in SS at postoperative 3rd month was found as 48.6%. In the separate patient groups, this rate was 74.1% (Group 1A), 29% (Group 1B), 49% (Group 2A), or 42% (Group 2B). Significant improvements were observed in the groups (p <0.001) other than Group 1B.

There are controversial results in the literature about the effect of preoperative SS and DO on the postoperative SS. Seki et al. have shown that DO was an independent predictor of postoperative restoration and that a severe preoperative SS score adversely affects the postoperative QoL score (4). Machino et al. reported that the cases with persistent DO had detrusor instability at a rate of 60% in the preoperative period (5). Similarly, Antunes et al. reported 66.7% persistence of preoperative DO complaints in the postoperative period (6).

There are also studies showing that SS scores other than urodynamic DO are also useful in predicting postoperative outcomes. In a retrospective study by Zhao et al. involving 128 BPH patients, the outcomes of patients with mild preoperative SS were shown to be much better than those with moderate and severe symptoms (7). In Choi et al.'s study with 116 patients, multivariate analysis has shown that poor initial SS were a risk factor for persistent SS in the postoperative period (OR=8.32) (10). In a study by Porru et al. including 60 patients, postoperative symptom scores were shown to get worse in patients with significant preoperative SS (p=0.001) (11).

Thus, we considered high SS scores as the preoperative risk factor in our patients rather than the presence of urodynamic DO and we did not perform urodynamic studies in the lack of absolute indications. Furthermore, it has been shown that SS strongly correlate with the urodynamic OD [10, 11, 13, and 21]. İn parallel with, postoperative storage complaints were found higher in patients with significant preoperative storage complaints in our study, (p <0.001). In contrast, some other studies have reported that preoperative DO does not predict postoperative SS (16, 17).

When we address the issue of de novo SS, it is known that post-TURP SS continues in 20-25% or even appears de novo (3). Similarly, the rate of de novo SS was observed in 22% of our pa-

tients. Permanent changes due to BOO in the bladder were proposed among the possible mechanisms for de novo SS (18). Persistence of DO was found in the elderly cases, in a previous study and they explain this situation by the aging bladder that may lead to functional change and persistent DO symptoms (6). However, we did not observe an effect of age on persistent SS in our study (p=0.34).

In one study, a correlation has been found between prostatic size and postoperative storage symptom severity, suggesting that patients with small prostate (less than 30g) are under risk (19). Similarly in our study, there were significant differences in term of prostatic volumes (mL) (p <0.003), preoperative S-IPSS scores (<0.001), preoperative Qmax values (mL/sec) (p<0.001) but such a relationship was found only in patients with de novo SS, not others (p=0.9).

Because of small prostate it may be argued that the cause of underlying pathology is OAB rather than BOO in the group 1B to explain their LUTS. And the statistical differentiation in the prostatic volume may reflect the fact that the underlying pathology is not the prostate, but rather the problem. Without urodynamics (cystometrogram and pressure flow study), this is unclear. And it does not change the fact that it seems medical therapy helps improve postoperative LUTS. But, in addition to the improvement of storage symptoms, excellent improvement was seen in the voiding symptoms after TURP (P <0.001). And the mean prostatic volume and PVR (47.2±15.6gr 49.04±9.3cc, respectively) were greater than normal reference values in group 1 and there is not difference between the two groups in term of Qmax (p=0.097). These suggested that underlying pathology may not only be OAB but also BOO.

When we compare the groups that received medical treatment, the rate of patients with de novo SS was different between G2A and G2B 30% and 33.3%, respectively, but not statistically significant (p=0.8). It means that the effect of solifenacin on de novo SS in this group is not clear, which might be explained by the small sample size of the subgroups.

Nocturia has been recognized as one of the most bothersome symptoms of LUTS/BPO and adversely affects the quality of life. Previous studies have convincingly shown that TURP has beneficial effect on nocturia (4, 13). In the current study, nocturia symptoms were significantly decreased in all groups after the operation (p <0.001). The pairwise comparison of the groups showed that there was significant difference between group 1A and group 1B in the postoperative period (p=0.024) whereas there was no difference between groups 2A and 2B (p=0.251). These results led us to think that the patients with high preoperative nocturia and S-IPSS scores may be under risk for postoperative nocturia symptoms and that early medical treatment adds extra benefit in high-risk patients.

When we investigate other intra-operatorative factors for post TURP SS, bipolar TURP has previously been shown to reduce postoperative SS (20). In our study, however, there was no significant difference between the two energy sources (p=0.6). In one study examining the effect of the pathology involved on SS, Nunzio et al. found a 55% reduction after TURP in the storage symptoms of patients with chronic prostatitis pathology (21). However, no such difference was found in our study (p=0.6).

Antimuscarinics are the first-line treatment for SS in men (22). We used 5mg solifenacin succinate as a prophylactic treatment on postoperative SS in different groups, which have been shown to be effective in OAB treatment. The improvement in postoperative SS of patients in Group 1A who used solifenacin, was significantly higher than in Group 1B (medication-free group) (p<0.001). However, solifenacin use did not result in significant improvement in postoperative SS in patients of Group 2 whose preoperative SS were not obvious (p <0.522). This result suggests that SS may be frequent in patients with preoperative SS, and that early initiation of anticholinergic treatment is beneficial only in this group of patients, but not for other patients.

Only a few studies have been found investigating the benefit of early medical treatment for the prevention of postoperative SS. Iselin et al. have shown that early oxybutynin treatment after TURP improved SS in the first week except for nocturia (23). In a randomized study, Tehranci

et al. found that postoperative treatment with tolterodine 2mg twice daily had significantly improved SS after TURP compared with placebo and reduced the need for analgesics (p=0.001 and p=0.036, respectively) without a significant difference in side effects (24). Shin et al. compared the patients who underwent TURP with no postoperative medical treatment (Group 1), with postoperative tamsulosin 0.2mg per day (Group 2), and postoperative solifenacin 5mg+tamsulosin 0.2mg per day (Group 3). They found that SS were lower in Group 3 compared to Group 2, but the improvements in storage and voiding symptoms and QoL in Groups 2 and 3 were not significantly different than Group 1 (25).

In all three studies above-mentioned, randomized treatment was initiated to eliminate that may occur after TURP. However, the initiation of medical treatment not randomly but in patients who most likely will develop these symptoms would be more rational both in terms of efficacy, cost effectiveness and safety. From this point of view, our study is the first to examine the benefit of the early postoperative treatment started only in the patients with severe SS development risk. In our study, postoperative SS in Group 1A, which received anticholinergic treatment, were found to be significantly lower than in Group 1B, which did not receive treatment. However, no such difference was observed between Group 2A (with treatment) and Group 2B (without treatment), both of which did not have significant SS in the preoperative period. This clearly demonstrates that it would be more beneficial to give early medical treatment only to the patient group with preoperative SS. However, no significant difference was found between groups A and B in terms of treatment--related improvements in the PVR.

The limitations of this study were as follows: the study was conducted at a single center, urodynamic studies were not performed in preoperative and postoperative periods routinely, small number of patients, and relatively short follow-up time. Finally, we did not use a specific questionnaire focusing on urgency symptoms such as the OABSS (Overactive Bladder Symptom Score).

CONCLUSIONS

TURP provides significant improvement in both storage and voiding symptoms. Severe preoperative S-İPSS scores have a predictive value for the storage complaints after TURP. Small prostate may predict postoperative SS and reflect the underlying OAB related pathology in the patients with de novo SS. With this in mind, 5mg solifenacin succinate treatment started early in the postoperative period seems to be beneficial only in patients with significant preoperative storage complaints but not in others.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Obesity: An independent protective factor for localized renal cell carcinoma in a systemic inflammation state

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ABSTRACT

Objectives: To explore the prognostic value of obesity (measured by BMI) on RCC in a systemic inflammation state.
Patients and Methods: Clinicopathological and hematological data of 540 surgically treated Chinese localized RCC patients between 2005 and 2010 were retrospectively collected. Found by receiver operating characteristic (ROC) curve for cancer-specific survival (CSS), the optimal cutoff values of neutrophil-lymphocyte ratio (NLR, an indicator of systemic inflammation state) and BMI were 2.12 and 23.32, respectively. Survival curves were drawn using Kaplan-Meier method. Univariate and multivariate Cox regression analyses were used to evaluate the prognostic value of BMI in localized RCC patients with different NLR.
Results: Overall, 36 patients died with a median follow-up of 70 months. Median overall survival (OS) was 66 months and the 5-year OS rate was 92.7%. In the multivariate analysis of total patients, higher BMI was an independent protective factor for CSS in total patients (p=0.048). While in systemic inflammation subgroup (high NLR subgroup) patients, higher BMI (obesity) turned out to be an independent protective factor for both CSS (p=0.025) and RFS (p=0.048).
Conclusion: In localized RCC patients, obesity was an independent protective factor for CSS and RFS in a systemic inflammation state.

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INTRODUCTION

Renal cell carcinoma (RCC) is the most common malignancy of kidney, accounting for 2%-3% of all adult malignancies (1). 20%-40% of localized RCC patients still suffered from cancer recurrence or metastasis even after surgery treatment, despite the significant improvement of RCC therapy (2). Thus, it is of importance to find effective prognostic factors to facilitate progress in treatment strategy.

Obesity is a widely accepted risk factor for the onset of RCC (3, 4). As an indicator of obesity, body mass index (BMI) was widely studied for its effect on the prognosis of RCC. Nevertheless, although obesity increases the incidence of RCC, several previous studies have shown that RCC patients with higher BMI at diagnosis might have better survival outcomes than those with normal or lower BMI levels (5-7). However, some investigators fail to confirm the existence of such association (8, 9). Although increasing evidence supports that higher

BMI is a favorable prognostic factor of RCC, this topic has not been thoroughly explored.

Increased neutrophil-lymphocyte ratio (NLR) is significantly associated with insulin resistance (IR), which is considered the common cause of impaired glucose tolerance, diabetes, dyslipidemia, hypertensive diseases and obesity (10). And accumulating evidence suggests that high NLR might be an adverse prognostic factor in metastatic RCC patients treated with interferon, interleukin-2 or sunitinib (11-13). However, studies regarding the prognostic value of NLR in non-metastatic RCC remain sparse.

NLR is an easily accessible index and high NLR has been proposed as an indicator of systemic inflammatory response, which is independently associated with clinical outcomes of various cancers (14). A systemic inflammatory state may be established long before metastases become clinically evident (15). Thus, it is of importance to study the prognostic effect of BMI under systemic inflammation state.

MATERIALS AND METHODS

Study population

Our retrospective study included 540 patients with localized renal cell carcinoma who underwent curative surgeries in Peking University First Hospital between 2005 and 2010. Patient's collection was based on the following inclusion criteria: (1) patients who were pathologically diagnosed with localized RCC (pT1-2N0M0, p: pathological grading) after surgery, (2) patients with complete information about BMI and NLR, (3) patients who had at least one effective follow--up. Patients were excluded if they had any of the following condition: (1) patients with previously diagnosed cancers or autoimmune diseases, (2) patients with incomplete clinical or pathological data, (3) patients who underwent previous chemotherapy and/or radiation therapy. This study was approved by the institutional ethics committee of Peking University First Hospital. As a retrospective analysis of routine data, a waiver of written informed consent was granted from the ethics committee. Patient records/information was anonymized and de-identified prior to analysis.

Clinical and pathological data collection

Clinicopathological and hematological data including gender (female or male), age (years old), height (m), weight (kg), cancer related symptoms (absent or present), histological subtype (clear cell or non-clear cell), Fuhrman nuclear grade (1-2 or 3-4), tumor necrosis (no or yes), tumor laterality (left or right), tumor size (≤7cm or >7cm, equals to T1 or T2 in TNM staging system), surgical procedures (partial or radical), neutrophil counts and lymphocyte counts were collected from medical records in the Department of Urology, Peking University First Hospital. Pathological TNM stage for each RCC was determined according to the AJCC 2002 TNM staging system. Patients were closely followed up after discharge with regular post-operative tests. BMI (kg/m^2) was calculated based on the measurements of height and weight at diagnosis. NLR was calculated as preoperative neutrophil counts divided by lymphocyte counts. The optimal cut-off value of BMI (23.32) and NLR (2.12) were determined according to the receiver operating characteristic (ROC) curves (shown in supplementary Figures S.1 and S.2 of cancer-specific survival (CSS). According to the Asian and Chinese standard of obesity, the normal ceiling of BMI is 23-24 (16, 17), and our cut-off value (23.32) falls in this range.

Indicators of prognosis

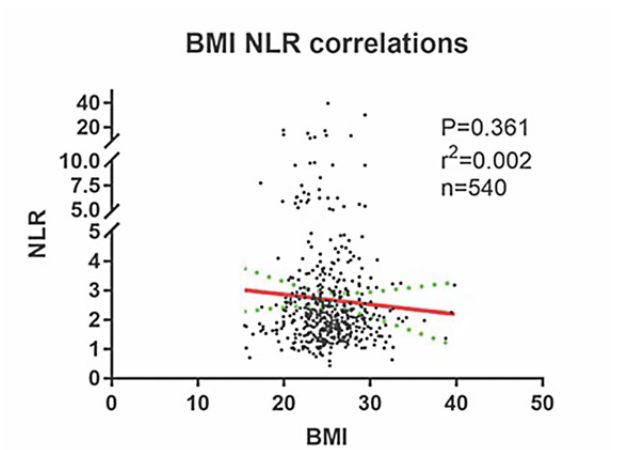
Overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS) were used as indicators of prognosis of the localized RCC patients in the study. OS, CSS, RFS were the intervals between the date of surgery treatment and (1) the date of death or last follow--up, (2) cancer-related death or last follow-up, (3) radiologic or histological confirmation of cancer recurrence or last follow-up.

Statistical analysis

The clinicopathological characteristics between groups with different BMI were compared using chi-square test. Kaplan-Meier survival curves were compared by using the log-rank test. BMI and other variables with $P < 0.1$ in univariate analysis were included in the multivaria-

te Cox proportional hazards regression model, and P <0.05 (labeled with '*') was regarded as statistically significant. Also, by using Cox proportional hazards regression models, we obtained the hazard ratios (HRs) and 95% confidence intervals (CIs) from the survival time. Data were analyzed using IBM SPSS statistics software (version 22.0, SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Pictures were drawn by GraphPad Prism (version7, Graphpad software, Inc., La Jolla, CA, USA, Figure 1) and IBM SPSS statistics software (Figure-2).

Figure 1 - Correlation analysis between BMI and NLR.



No correlation could be found between BMI and NLR (p >0.05).
Abbreviation: **BMI** = body mass index, **NLR** = neutrophil-lymphocyte ratio

RESULTS

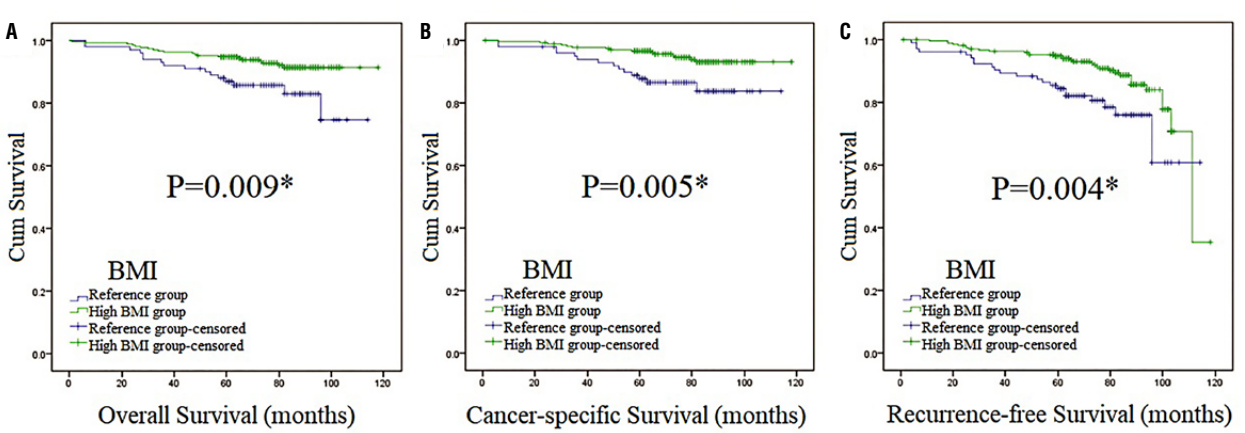
Cohort characteristics

In total, 400 men and 140 women with localized RCC were included in the study with a mean age of 54±13.4 years old. 48.3% (261/540) of the tumors were located on the left side. Only 53 (9.8%) patients manifested cancer related symptoms (backache, hematuria and/or abdominal mass). Most patients (88.9%, 480/540) suffered from clear cell carcinoma. Patients whose tumor size was bigger than 7cm accounted for less than 10%. Using 23.32 as the cutoff value of BMI, 145 (26.9%) and 395 (73.1%) patients were respectively stratified into the reference group (low BMI group BMI <23.32) and high BMI group (BMI ≥23.32). Differences in gender were found between reference group and high BMI group p=0.006). No differences were found between reference group and high BMI group in terms of age, tumor laterality, cancer related symptoms presence, histology, tumor size, Fuhrman nuclear grade, tumor necrosis or NLR. 283 and 257 patients were respectively categorized into low and high NLR group, according to the cutoff value of NLR at 2.12 (Table-1). Correlation analysis found no correlation between NLR and BMI (Figure-1).

Survival analysis on BMI and NLR

We used OS, CSS and RFS as the indicators of prognosis to estimate the association of BMI

Figure 2 - Survival curves stratified by BMI at the level of 23.32 in total patients (Kaplan-Meier method).



Survival curves of OS (Figure 2A), CSS (Figure 2B) and RFS (Figure 2C) in total patients.
*:p <0.05; Abbreviation: BMI=body mass index

Table 1 - Distribution of clinicopathological factors stratified by preoperative BMI.

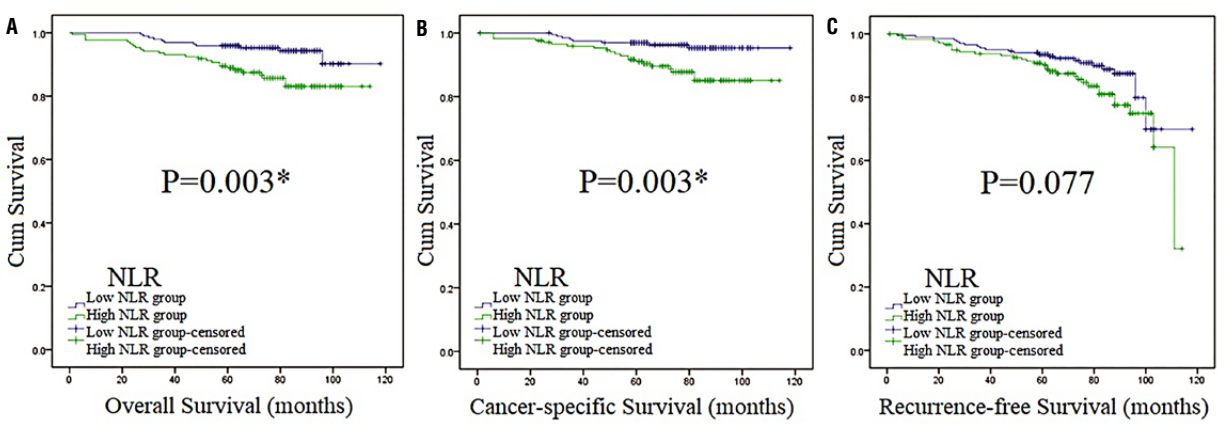
Characteristics	All patients	BMI<23.32	BMI≥23.32	P value
	N=540 (N%)	N=145 (N%)	N=395 (N%)	
Age				**0.184**
<60	352 (65.2)	88 (60.7)	264 (66.8)	
≥60	188 (34.8)	57 (39.3)	131 (33.2)	
Gender				**0.006***
Male	400 (74.1)	95 (65.5)	305 (77.2)	
Female	140 (25.9)	50 (34.5)	90 (22.8)	
Tumor laterality				**0.428**
Left	261 (48.3)	66 (45.5)	195 (49.4)	
Right	279 (51.7)	79 (54.5)	200 (50.6)	
Cancer related symptoms				**0.219**
Absent	487 (90.2)	127 (87.6)	360 (91.1)	
Present	53 (9.8)	18 (12.4)	35 (8.9)	
Surgical procedures				
Partial resection	157 (29.1)	40 (27.6)	118 (29.9)	**0.605**
Radical resection	383 (70.9)	105 (72.4)	277 (70.1)	
Histology				**0.131**
Clear cell	480 (88.9)	124 (85.5)	356 (90.1)	
Non-clear cell	60 (11.1)	21 (14.5)	39 (9.9)	
Tumor size				**0.066**
≤7 (T1N0M0)	496 (91.9)	128 (88.3)	368 (93.2)	
>7 (T2N0M0)	44 (8.1)	17 (11.7)	27 (6.8)	
Fuhrman Grade				**0.085**
1-2	479 (88.7)	123 (84.8)	356 (90.1)	
3-4	61 (11.3)	22 (15.2)	39 (9.9)	
Tumor necrosis				**0.163**
Absent	462 (85.6)	119 (82.1)	343 (86.8)	
Present	78 (14.4)	26 (17.9)	52 (13.2)	
NLR				**0.244**
≤2.12	283 (52.4)	70 (48.3)	213 (53.9)	
>2.12	257 (47.6)	75 (51.7)	182 (46.1)	

*:$p<0.05$; Abbreviations: **BMI**=body mass index; **NLR**=neutrophil-lymphocyte ratio.

The data of histology, tumor size, Fuhrman Grade and tumor necrosis were obtained from pathological findings of surgical specimens.

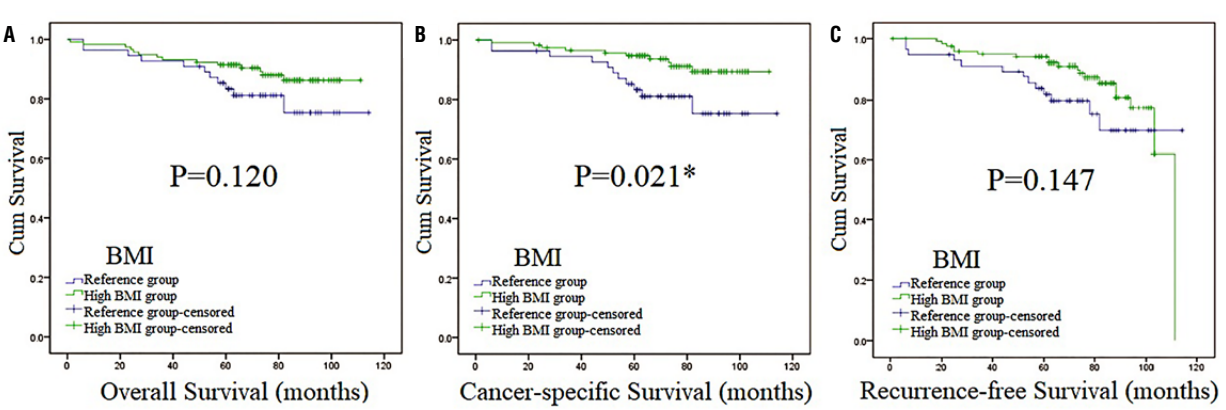
and the clinical outcomes of patients with localized RCC. The median follow-up was 70 months (in the range of 1-118). Overall, 36 patients died, with 16 and 20 in the reference group and high BMI group, respectively. Median OS was 66 months (in the range of 1-118) and the 5-year OS rate was 92.7%. Kaplan--Meier (K-M) curves indicated that differences were found between reference group and high BMI group in OS, CSS and RFS, establishing that BMI was associated with OS, CSS and RFS in our study (Figure-2). Also, high BMI group had higher survival curves of OS, CSS and RFS than the reference group, which indicated that high BMI group might have better OS, CSS and RFS. On the other hand, patients with high NLR had worse OS and CSS than low NLR according to survival curves (Figure-3), which indicated they had worse OS and CSS. Then, subgroup analysis was performed by stratifying subjects by NLR at the level of 2.12. As we could see in Figure-S.3, BMI was associated with RFS (p=0.010). While in high NLR group patients (Figure 4), association was found between BMI and CSS (p=0.021). In Figure-5, K-M curves were drawn using a combination of BMI and NLR, of which high BMI-low NLR subgroup had best survival outcomes, while low BMI-high NLR subgroup was the worst.

Figure 3 - Survival curves stratified by NLR at the level of 2.12 in total patients (Kaplan-Meier method).



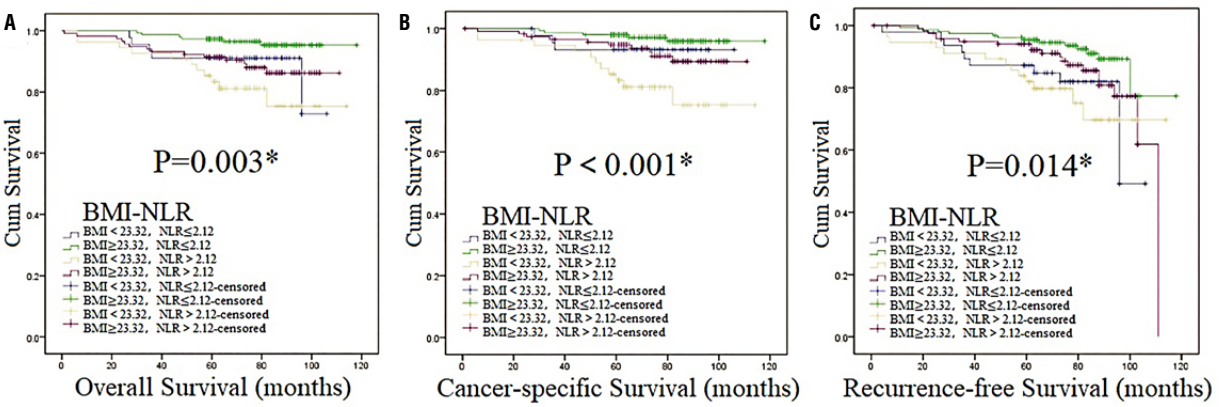
Survival curves of OS (Figure 3A), CSS (Figure 3B) and RFS (Figure 3C) in total patients.
Abbreviation: **NLR** = neutrophil-lymphocyte ratio.
*:p <0.05

Figure 4 - Survival curves stratified by BMI at the level of 23.32 in high NLR patients (Kaplan-Meier method).



Survival curves of OS (Figure 4A), CSS (Figure 4B) and RFS (Figure 4C) in high NLR patients.
Abbreviations: **BMI**=body mass index; **NLR**=neutrophil-lymphocyte ratio.
*:p <0.05

Figure 5 - Survival curves stratified by BMI-NLR at the level of 23.32 (BMI) and 2.12 (NLR) in total patients (Kaplan-Meier method).



Survival curves of OS (Figure 5A), CSS (Figure 5B) and RFS (Figure 5C) in total patients.
Abbreviations: **BMI**=body mass index; **NLR**=neutrophil-lymphocyte ratio.
*:p <0.05

Univariate and multivariate analysis

Univariate Cox regression analyses of factors for OS, CSS and RFS were shown in Tables 2-4. In univariate analysis of total patients, larger tumor size (>7 vs. ≤7cm) and lower BMI (<23.32 vs. ≥23.32) were associated with poorer OS, CSS and RFS (all p <0.05). Older age (≥60 vs. <60 years) and higher NLR (>2.12 vs. ≤2.12) were correlated with lower OS (p <0.001, p=0.005, respectively) and CSS (p=0.003, p=0.005, respectively). Presence of cancer related symptoms was associated with worse CSS (p=0.012) and RFS (p=0.001). Radical nephrectomy (radical vs. partial) and higher Fuhrman grade (3-4 vs. 1-2) were correlated with poorer OS (p=0.047, p=0.004, respectively) and RFS (p <0.030, p <0.001, respectively). Gender, tumor laterality, histology and tumor necrosis were not associated with OS, CSS or RFS (all p >0.05).

Subgroup univariate analysis revealed that in low NLR group patients, older age remained its association with lower OS (p=0.004) and CSS (p=0.024). Higher Fuhrman nuclear grade had correlation with poorer OS (p=0.030) and RFS (p=0.001). Larger BMI value was associated with better RFS (p=0.014). While in high NLR group (systemic inflammation state) patients, older age was associated with worse OS (p=0.027). Manifestation of cancer related symptoms and larger tumor size were correlated with worse CSS (p=0.027, p=0.038, respectively) and RFS (both p <0.001), but not OS. Radical nephrectomy (radical vs. partial) was associated with poorer RFS (p=0.043). Larger BMI value was correlated with better CSS (p=0.027).

Outcomes of multivariate Cox regression analysis of OS, CSS and RFS are listed in Tables 2-4. In the multivariate analysis of total patients, manifestation of cancer related symptoms and larger tumor size were independent risk factors for OS (p=0.015; p=0.045, respectively), CSS (p=0.003; p=0.023, respectively) and RFS (p=0.006; p <0.001, respectively). Older age and higher NLR had independent adverse effects on OS (p <0.001; p =0.006, respectively) and CSS (p=0.003; p=0.005, respectively). While higher BMI was only an independent protective factor for CSS (HR=0.474, 95%CI: 0.226-0.994, p=0.048).

Furthermore, subgroup multivariate analysis turned out that in low NLR subgroup, older age was an independent risk factor for OS (p=0.005) and CSS (p=0.024), higher Fuhrman grade was an independent adverse predictor for OS (p=0.0499) and RFS (p=0.001). While in high NLR group (systemic inflammation state) patients, presence of cancer related symptoms and larger tumor size became independent risk factors for

Table 2 - Univariate and multivariate analysis of OS in total patients, low NLR and high NLR subgroups.

Characteristics	Total				Low NLR				High NLR (systemic inflammation state)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Gender (female vs. male)	0.574 (0.252-1.311)	0.188			0.790 (0.210-2.978)	0.728			0.517 (0.177-1.507)	0.227		
Age (<60 vs. ≥60)	3.734 (1.867-7.468)	<0.001*	4.010 (1.987-8.091)	<0.001	9.482 (2.048-43.911)	0.004*	9.040 (1.948-41.949)	0.005*	2.471 (1.110-5.501)	0.027*	3.348 (1.424-7.873)	0.006*
Tumor laterality (left vs. right)	1.417 (0.730-2.749)	0.303			1.330 (0.406-4.361)	0.638			1.379 (0.619-3.072)	0.431		
Cancer related symptoms (absent vs. present)	2.322 (0.965-5.589)	0.06	3.073 (1.241-7.614)	0.015*	2.116 (0.455-9.828)	0.339			2.736 (0.938-7.978)	0.065	3.872 (1.263-11.869)	0.018*
Surgical procedures (partial vs. radical)	2.603 (1.012-6.699)	0.047*			5.677 (0.726-44.349)	0.098			1.465 (0.503-4.271)	0.484		
Tumor size (≤7 vs. >7)	2.778 (1.156-6.677)	0.022*	2.483 (1.022-6.030)	0.045*	2.358 (0.302-18.444)	0.414			2.290 (0.859-6.108)	0.098	2.856 (1.047-7.793)	0.040*
Histology (clear cell vs. non-clear cell)	1.085 (0.384-3.070)	0.877			0.675 (0.146-3.131)	0.616			1.424 (0.336-6.040)	0.632		
Tumor necrosis (no vs yes)	1.563 (0.684-3.573)	0.29			3.346 (0.879-12.731)	0.077			0.935 (0.321-2.726)	0.902		
Fuhrman grade (1-2 vs. 3-4)	3.051 (1.433-6.498)	0.004*			4.377 (1.153-16.615)	0.030*	3.887 (1.001-15.098)	0.0499*	2.200 (0.877-5.520)	0.093		
NLR (≤2.12 vs. >2.12)	2.762 (1.359-5.614)	0.005*	2.761 (1.340-5.690)	0.006*								
BMI (<23.32 vs.≥ 23.32)	0.428 (0.222-0.828)	0.012*			0.334 (0.102-1.097)	0.071			0.540 (0.244-1.191)	0.127		

*: $p < 0.05$; Abbreviations: **BMI**=body mass index; **NLR**=neutrophil-lymphocyte ratio; **HR**=hazard ratio; **CI**=confidence interval; **OS**=overall survival; /=not significant; **Blank space**=not done.

Table 3 - Univariate and multivariate analysis of CSS in total patients, low NLR and high NLR subgroups.

Characteristics	Total				Low NLR				High NLR (systemic inflammation state)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Gender (female vs. male)	0.752 (0.321-1.761)	0.511			0.711 (0.143-3.522)	0.676			0.839 (0.307-2.292)	0.732		
Age (<60 vs. ≥ 60)	3.084 (1.456-6.530)	0.003*	3.024 (1.339-6.827)	0.003*	6.326 (1.276-31.365)	0.024*	6.326 (1.276-31.365)	0.024*	2.198 (0.926-5.218)	0.074	2.991 (1.165-7.682)	0.023*
Tumor laterality (left vs. right)	1.251 (0.602-2.601)	0.549			1.103 (0.276-4.414)	0.89			1.236 (0.521-2.936)	0.631		
Cancer related symptoms (absent vs. present)	3.146 (1.280-6.847)	0.012*	4.597 (1.746-12.101)	0.003*	3.328 (0.669-16.547)	0.142			3.415 (1.148-10.164)	0.027*	5.285 (1.624-17.200)	0.006*
Surgical procedures (partial vs. radical)	2.599 (0.904-7.469)	0.076			3.851 (0.474-31.308)	0.207			1.689 (0.497-5.736)	0.401		
Tumor size (≤7 vs. >7)	3.641 (1.481-8.949)	0.005*	2.889 (1.160-7.195)	0.023*	3.363 (0.413-27.387)	0.257			2.901 (1.061-7.930)	0.038*	3.968 (1.420-11.086)	0.009*
Histology (clear cell vs. non-clear cell)	1.168 (0.353-3.859)	0.799			0.435 (0.088-2.156)	0.308			2.484 (0.333-18.514)	0.375		
Tumor necrosis (no vs yes)	1.032 (0.359-2.969)	0.953			2.802 (0.563-13.933)	0.208			0.521 (0.121-2.237)	0.38		
Fuhrman grade (1-2 vs. 3-4)	2.410 (0.980-5.928)	0.055			4.076 (0.821-20.242)	0.086			1.622 (0.544-4.831)	0.385		
NLR (≤2.12 vs. >2.12)	3.212 (1.422-7.254)	0.005*	3.360 (1.453-7.769)	0.005*								
BMI (<23.32 vs.≥ 23.32)	0.363 (0.175-0.753)	0.006*	0.474 (0.226-0.994)	0.048*	0.461 (0.110-1.933)	0.29			0.378 (0.160-0.893)	0.027*	0.367 (0.153-0.879)	0.025*

*:p<0.05; Abbreviations: **BMI**=body mass index; **NLR**=neutrophil-lymphocyte ratio; **HR**=hazard ratio; **CI**=confidence interval; **CSS**=cancer specific survival; /=not significant; **Blank space**=not done.

Table 4 - Univariate and multivariate analysis of RFS in total patients, low NLR and high NLR subgroups.

Characteristics	Total				Low NLR				High NLR (systemic inflammation state)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Gender (female vs. male)	0.707 (0.380-1.315)	0.273			0.836 (0.346-2.022)	0.692			0.613 (0.251-1.469)	0.282		
Age (<60 vs. ≥ 60)	1.494 (0.876-2.548)	0.14			2.277 (1.019-5.088)	0.045			1.027 (0.498-2.117)	0.943		
Tumor laterality (left vs. right)	0.922 (0.545-1.558)	0.761			1.065 (0.478-2.371)	0.878			0.840 (0.419-1.685)	0.624		
Cancer related symptoms (absent vs. present)	3.065 (1.610-5.833)	0.001*	2.501 (1.294-4.836)	0.006*	2.061 (0.701-6.055)	0.189			4.429 (1.968-9.967)	<0.001*t	5.671 (2.393-13.440)	<0.001*
Surgical procedures (partial vs. radical)	2.210 (1.080-4.522)	0.030*			1.370 (0.567-3.312)	0.484			4.398 (1.046-18.500)	0.043*	4.151 (0.929-18.545)	0.062
Tumor size (≤7 vs. >7)	4.823 (2.656-8.757)	<0.001*	3.837 (2.048-7.187)	<0.001*	3.049 (0.900-10.332)	0.073			5.737 (2.757-11.937)	<0.001*	4.574 (2.125-9.848)	<0.001*
Histology (clear cell vs. non-clear cell)	1.769 (0.639-4.897)	0.273			1.134 (0.336-3.825)	0.84			3.706 (0.505-27.184)	0.198		
Tumor necrosis (no vs yes)	1.476 (0.741-2.941)	0.268			2.602 (0.955-7.094)	0.062			0.911 (0.346-2.402)	0.851		
Fuhrman grade (1-2 vs. 3-4)	2.957 (1.626-5.378)	<0.001*	1.990 (1.051-3.768)	0.035*	4.923 (1.996-12.144)	0.001*	4.923 (1.996-12.144)	0.001*	1.885 (0.833-4.266)	0.128		
NLR (≤2.12 vs. >2.12)	1.604 (0.944-2.726)	0.081										
BMI (<23.32 vs.≥ 23.32)	0.467 (0.274-0.797)	0.005*			0.358 (0.157-0.815)	0.014*			0.595 (0.292-1.211)	0.152	0.477 (0.229-0.994)	0.048*

*:*p*<0.05; Abbreviations: **BMI**=body mass index; **NLR**=neutrophil-lymphocyte ratio; **HR**=hazard ratio; **CI**=confidence interval; **RFS**=recurrence-free survival; /=not significant; **Blank space**=not done.

OS, CSS and RFS (cancer related symptoms presence: p=0.018, p=0.006, p <0.001, respectively; tumor size: p=0.040, p=0.009, p <0.001, respectively). Also, older age was an independent adverse predictor for OS (p=0.006) and CSS (p=0.023). Interestingly, higher BMI turned out to be an independent protective factor for CSS (HR=0.367, 95%CI: 0.153-0.879, p=0.025) and RFS (HR=0.477, 95%CI: 0.229-0.994, p=0.048) in high NLR group (systemic inflammation state) patients.

DISCUSSION

This study evaluated the prognostic value of BMI both in total patients and in systemic inflammation state patients. To the best of our knowledge, this is the first study to explore the prognostic value of obesity for localized renal cell carcinoma in a systemic inflammation state.

BMI and RCC prognosis

Obesity has emerged as a significant adverse predictor for RCC in previous studies. People with an increased BMI have two to three folds increased risk for developing RCC (18). The hypothetical explanations for the increased risk included the alteration of the insulin-like growth factor system, lipid peroxidation, high levels of estrogen, hypertension and the malfunction of immune system. However, there seems to be a paradox: obesity increases the risk of RCC but in the meantime, it is associated with improved tumor prognosis. In our study, obesity was an independent favorable prognostic factor for CSS in total patients. The results were in line with some Asian studies. Jeon et al. found overweight and obese Korean patients with RCC had more favorable prognosis than those with a normal BMI (19). Similar researches by Awakura et al. also reported that a BMI of 23kg/m^2 or more favorably affected the prognosis of Japanese RCC subjects, although BMI did not differ significantly with respect to stage or grade (20).

Similar results have also been obtained in some studies about western RCC patients. Yu et al. suggested that prognosis was no worse and may even be better among obese patients with RCC (21). In a study of 400 patients with non-metastatic, node-negative RCC conducted by Kamat et al., overweight and obese patients had a more favorable prognosis than patients with a normal BMI (7). In a study composed of 970 clear cell RCC patients, Parker et al. reported that high BMI was associated with negative lymph nodes and the absence of metastases (5).

Some hypotheses had been proposed to explain the contradiction. Patients with higher BMI might have better nutritional status and potential survival advantage (22). RCC developed in the obese might represent biologically distinct and less aggressive tumors versus those with normal weight (6, 23). Furthermore, patients with higher BMI were more likely to have contact with their physicians and have increased possibilities of early cancer detection (5).

The discovery of a new paradox inside the abovementioned paradox made the issue even more complicated. Bagheri et al. discovered through 8 studies of 8699 survivals that while CSS increased with BMI, when BMI is higher than 25, OS surprisingly decreased with BMI. Different causes of mortality had different directions after BMI reached a certain level, creating a 'paradox within a paradox' (24).

If we are to truly understand the role that BMI plays in RCC and other cancer patient, efforts are still needed to explicitly illustrate the issue in the future.

Systemic inflammation state and RCC prognosis

NLR has been recognized as the representative hematological index of systemic inflammation (14). However, studies about the prognostic value of the pretreatment NLR in non-metastatic RCC are sparse and with conflicting findings. Ohno et al. found that an increased NLR was an independent risk predictor for relapse-free survival in a small cohort of 192 RCC patients from Japan (25). Interestingly, Pichler et al. demonstrated that an increased NLR was an independent negative predictor for OS (26). Variance in study designs and sample sizes might bring about different outcomes. Considering the uncertainty of NLR's role in RCC patients, Hu performed a meta-analysis to assess the prognostic significance of high NLR for OS and RFS/PFS (progress-free survival), and found elevated NLR predicted poorer OS and RFS/PFS in patients with RCC (27).

As an index of systemic inflammation, high NLR might represent an inflammatory microenvironment which can increase mutation rates, in addition to enhancing the proliferation of mutated cells (28). High NLR is associated with high infiltration of tumor-associated macrophages (TAMs) which are identified to mediate refractoriness to anti-vascular endothelial growth factor (VEGF) treatment (29). Thus, that elevated NLR is related to poorer prognostic outcome of patients with RCC sounds reasonable. In Hu's meta-analysis, pooled analysis of studies showed NLR played a far more superior prognostic role with a cutoff value no more than 3 compared to higher than 3 (27). So, choosing 2.12 as the cutoff value seems applicable (In our study, the optimal cutoff value of NLR was 2.12 for CSS, calculated by ROC curve).

In this research, NLR was associated with OS and CSS in total patients in univariate and multivariate analyses, which showed that high NLR (systemic inflammation state) was independently associated with poor OS and CSS. Therefore, our findings are in support of the recognition that systemic inflammation state has a correlation with poor outcomes in RCC patients.

One aspect of importance is to distinguish systemic inflammation from chronic inflammation common in all obese people. Chronic inflammation happens because adipose tissue secretes pro-inflammatory cytokines, leading to a state of chronic low-grade inflammation associated with obesity, such that obese persons often experience higher concentrations of inflammatory biomarkers than their normal-weight counterparts (30). Systemic inflammation state in our research, however, is defined by high NLR (>2.12), which is a much more severe condition than chronic inflammation above.

Prognostic value of BMI in a systemic inflammation state

As can be inferred from discussion above, the prognostic value of BMI was greatly enhanced in a systemic inflammation state. Systemic inflammation state makes possible a favorable environment for cancer cells: infiltration and metastasis are relatively easier (31). Therefore, cancer patients will become particularly sensitive in this condition and react more fiercely to changes in a lot of conditions. BMI is one example. As discussed above, patients with higher BMI tend to be in better nutritional conditions and vice versa; the influence of BMI on prognosis is exponentially magnified in a systemic inflammation condition. The results of our study validated this hypothesis (Figure-5). In subgroup analyses of our study, BMI was an independent favorable factor for CSS and RFS in high NLR (systemic inflammation state) patients rather than in low NLR patients, which indicated that the prognostic value of BMI was increased in systemic inflammatory status.

Another possible explanation includes the change in the effects of proinflammatory cytokines in subjects with high BMI. This is the case because obese patients are known to be associated with a state of chronic inflammation (23). Cytokines including C-reactive protein (CRP), tumor necrosis factor (TNF), IL6 and IL18, among others already increased greatly these patients (32). When this is the case, the effect of systemic inflammation (marked by high NLR) is attenuated since the body is already accustomed to abundance in inflammation cytokines. Therefore, the difference between survival outcomes between high and low BMI patients is further magnified, making it an especially sensitive independent predictor in a high NLR environment.

There are still some limitations in our study. As a retrospective study, selection bias was inevitable for making certain inclusion criteria. Another limitation was the relatively small size of samples from one single medical center. Our findings should be interpreted with caution until they are validated in a large multi-institutional pooled analysis.

If our finding that higher NLR increases the prognostic value of BMI is confirmed, BMI and NLR might need to be incorporated into the equation when protocols for therapy in RCC patients are planned.

CONCLUSIONS

In localized RCC patients, BMI was an independent favorable factor for CSS. In subgroup

analyses, BMI was an independent protective factor for CSS in high NLR patients rather than in low NLR patients, which indicated that the prognostic value of BMI was increased in systemic inflammatory status.

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Zhenhua Liu and Haifeng Wang contributed equally to this research and should be both considered first author.

CONFLICT OF INTEREST

None declared.

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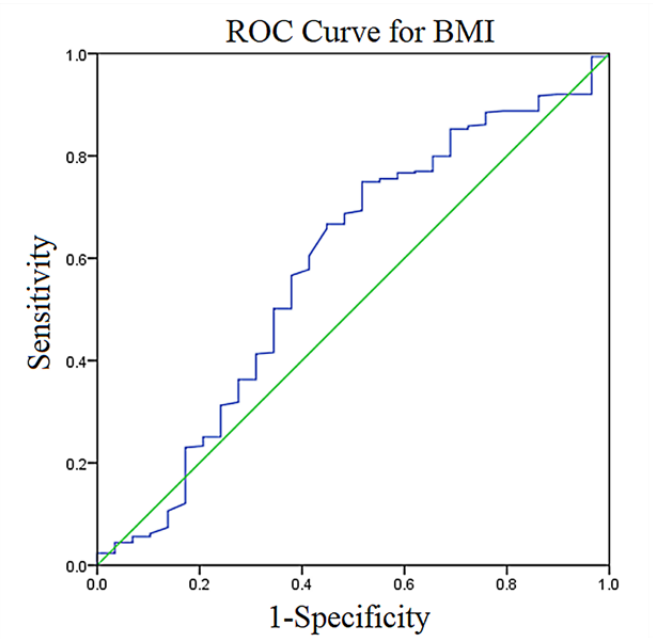
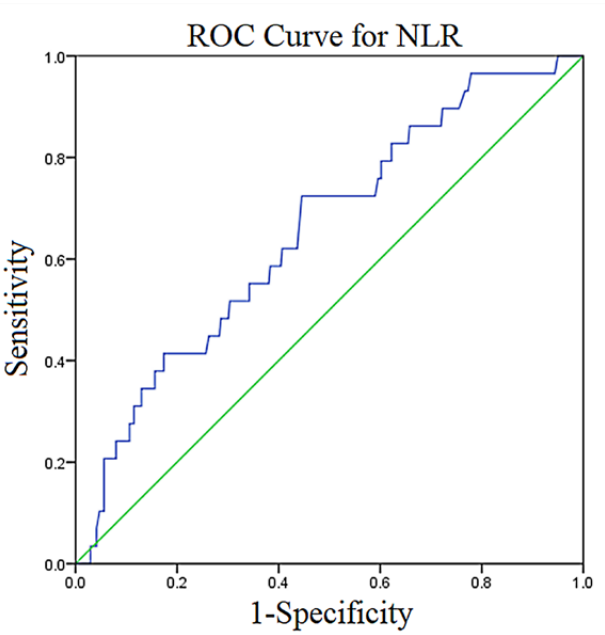
APPENDIX - Supplementary Figures

Figure-S.1 - Receiver operating characteristic (ROC) curve for BMI.



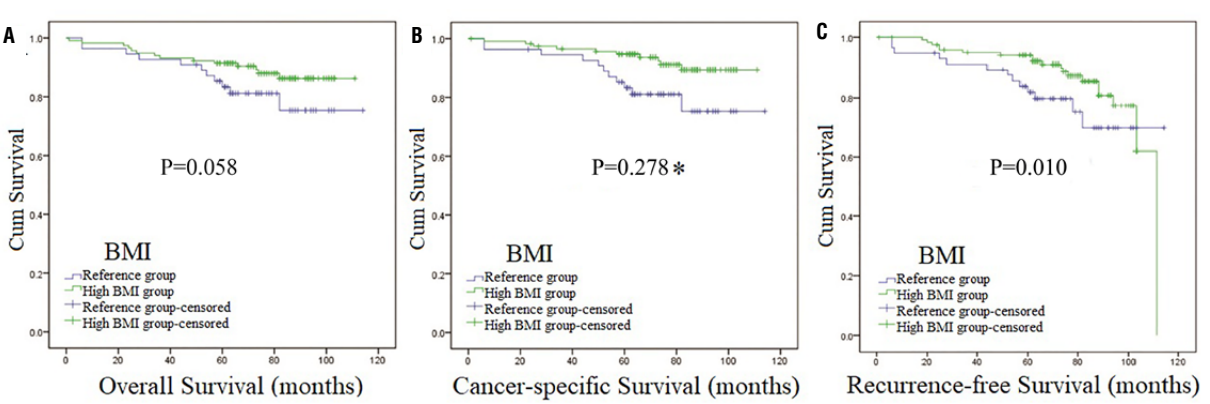
Abbreviations: **BMI**=body mass index.

Figure-S.2 - Receiver operating characteristic (ROC) curve for NLR.



Abbreviations: **NLR=**neutrophil-lymphocyte ratio.

Figure-S.3 - Survival curves stratified by BMI at the level of 23.32 in low NLR patients (Kaplan-Meier method).



Survival curves of OS (Figure S.3A), CSS (Figure S.3B) and RFS (Figure S.3C) in low NLR patients.
Abbreviations: **BMI**=body mass index; **NLR**=neutrophil-lymphocyte ratio.
*:p <0.0

ORIGINAL ARTICLE

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Overall survival prediction in metastatic castration-resistant prostate cancer treated with radium-223

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ABSTRACT

Objective: Radium-223(223Ra) is indicated for patients (p) with metastatic castration resistant prostate cancer (mCRCP). Objectives: The aim of this study was to evaluate the role of baseline clinical variables associated with overall survival (OS) and toxicity of 223Ra. Its purpose was to identify the factors that can predict a better response to treatment and provide information regarding the most appropriate time for the application of 223Ra.

Materials and Methods: Prospective study in 40p with mCRPC treated with 223Ra. End points were OS, progression-free survival and time to progression. The follow-up parameters were: doses received, hemoglobin (Hb), absolute neutrophil count (ANC), platelet count (PC), prostate specific antigen (PSA), alkaline phosphatase (ALP), Visual Analogue Scale for pain, Eastern Cooperative Oncology Group (ECOG) and WHO's Cancer Pain Ladder. The use of other treatments was also evaluated.

Results: Median OS was 17.1 months(mo) (CI95%6.5-27.7); 26/40p received complete treatment of 223Ra, without reaching a median OS and 14p received incomplete treatment with a median OS 13.6mo(CI95%1.6-25.6). Median follow-up was 11.2mo (range:1.3-45.2). The univariate analysis showed that factors as VAS, ECOG, Hb and ALP values were independently associated with OS. First line treatment with 223Ra was started in 11/40p, while 19p had been heavily pre-treated and 13p received concomitant treatment.

Conclusions: 223Ra therapy require an adequate selection of patients to obtain the greatest clinical benefit. Low basal Hb, hight basal ALP, bone marrow involvement and an altered ECOG were the main factors that decreased OS in our patients. 223Ra should be considered relatively early in the course of treatment.

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INTRODUCTION

The frequency of new cases of prostate cancer reported by The Global Cancer Observatory was 12.712 in Colombia for 2018 (1). Additionally, the incidence of metastatic castration-resistant prostate cancer (mCRPC) is increasing, of which the most common are bone metastases. Mortality secondary to mCRPC is related to the metastatic event, therefore, the increasing incidence of bone metastases represents an ideal target for improving outcomes. Bone metastases are a common cause of morbidity and mortality and pose a secondary economic burden on healthcare. Skeletal

related events (SREs) continue to be a major cause of disability, diminished quality of life (QoL), and increased cost for treatment of complications (2).

Until 2004, chemotherapy was the main treatment for mCRPC. Since then, different strategies have emerged with novel agents to manipulate the androgen-receptor, targeting the immune system and treating the bone micro-environment.

Traditionally, bone pain has been managed with analgesics, external beam radiation--therapy (EBRT), and beta-emitting radioisotopes. While some of the current standard treatments, such as bisphosphonates, rank ligand inhibitors, and bone-seeking beta-emitters like strontium, have been shown to length the progression time, none have demonstrated a survival advantage (3). The development of others agents, including cabazitaxel, cellular immunotherapy-(sipuleucel-T), androgen biosynthesis inhibitors-(abiraterone), androgen receptor antagonists-(enzalutamide), and targeted therapy for bone metastases with Radium-223 dichloride (223Ra) (4) have been of great benefit, but there is uncertainty regarding the optimal use of these treatments in sequence and in combination.

223Ra is the sixth novel agent to be added to the treatment of mCRPC, having been approved by the Food and Drug Administration on May, 2013, and this treatment was later incorporated into the National Comprehensive Cancer Network guidelines (5, 6). This approval was based on the results of the randomized, double-blinded, multinational clinical trial titled ALSYMPCA-(ALpharadin in SYMptomatic Prostate CAncer) (7).

ALSYMPCA compared 223Ra with placebo in men with mCRPC with symptomatic bone metastases and no visceral metastases. In this clinical trial incorporating 307 patients (p) in the placebo arm and 614p in the treatment arm. The clinical trial demonstrated a 3.6 month (mo) overall survival (OS) benefit with 223Ra, in comparison to the placebo (median14.9 vs.11.3mo HR 0.70, 95% CI: 0.58-0.83, p <0.001) (7).

223Ra is an alpha emitter and calcium--mimetic that targets the hydroxyapatite matrix in the bone, thereby accumulating in areas of active bone remodeling and formation, such as sites of osteoblastic bone metastases (8-10). Despite the increasing clinical use of 223Ra in mCRPC, clinical variables that may predict responses are still difficult to identify (11, 12). The aim of this single-center prospective study was to evaluate the role of baseline clinical variables associated with the OS and toxicity of 223Ra therapy. Its purpose was to identify the factors that can predict a better response to treatment and provide information regarding the most appropriate time for the application of 223Ra.

MATERIALS AND METHODS

Study design

This prospective study was conducted between November 2014 and April 2018 with 40p with mCRPC treated with 223Ra in the nuclear medicine department at Pablo Tobón Uribe Hospital. The study was approved by the local ethical committee and conducted in accordance with Helsinki Declaration.

Patients

Patients were included if they had bone pain, two or more bone metastases on bone--scintigraphy, and absence of visceral metastasis in thoracic and abdomino-pelvic-CT. Before the first administration of 223Ra, the absolute neutrophil count (ANC) was ≥1.5x109/L, hemoglobin (Hb) was ≥10g/dL, and the platelet count (PC) was ≥100x109/L. During subsequent administrations, the ANC was ≥1x109/L, and PC was ≥50x109/L.

223Ra treatment

223Ra is a emitting alpha-particle with a short range of 2-10 cell bodies (10µm) and a physical half-life of 11.43 days. It has a complicated decay scheme with a series of six daughter products before decaying to stable lead. The total emitted energy is 28.2 MeV, of which 93.5% are α-emissions (average energy of 5.78MeV), less than 3.6% is β-particle, and less than 1.1% are γ-emissions (154keV). This results in a low signal which can present challenges for quantitative imaging, but nevertheless, introduces the potential for individualized biodistribution studies. The treatment consisted of 6 cycles every 4 weeks. The standard dose is 55kBq/kg.

Evaluation and follow-up

Before and after treatment, the patients were clinically evaluated using Eastern Cooperative Oncology Group (ECOG), WHO's Cancer Pain Ladder (CPL) and Visual Analogue Scale for pain (VAS) to evaluate the level of functioning, the decrease in consumption of opioid analgesics, and the reduction of skeletal pain, respectively (Table-1). Bone-scintigraphy was achieved before and after 223Ra-treatment. Skeletal tumor burden was classified as low when the number of bone metastases was between 2-6, intermediate >6, and high burden in the presence of diffuse disease (superscan). Laboratory tests were assessed before, during, and after 223Ra treatment with ANC, Hb, PC, prostate specific antigen (PSA), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP). The use of chemotherapy, abiraterone, enzalutamide, bisphosphonates, and EBRT was also evaluated.

Response criteria

Response to treatment was defined as a sustained reduction in skeletal symptoms (VAS), an increase in the level of functioning (ECOG), a decrease in consumption of opioid analgesics (CPL), and a reduction in ALP levels between the first cycle and 1-3mo after the last cycle of 223Ra.

The response rate was defined in terms of ALP change, such as if there was a reduction >25%, if there was a reduction <25%, if there was an increase in ALP <25%, and if there was an increase in ALP levels >25%.

The main endpoint was OS, which was established as from initial 223Ra cycle until either the date of death from any cause or the last follow-up. Patients who were alive at the last follow-up date were censored. Other factors were evaluated, such as progression-free survival (PFS), which was established from initial 223Ra cycle until date of objective tumor progression, death by any cause, or last follow-up, and time to progression (TTP), which was assessed from the date of initial 223Ra cycle to date of objective tumor progression (defined as a lesion progressing in the bone, nodal or visceral lesions). Patients who were alive and did not experience an event (progression or SREs) were censored.

Table 1 - Classification of ECOG, CPL and VAS.

Visual analogue scale for pain (VAS)		WHO´s Cancer Pain Ladder (CPL)	
0	No	0	No pain. Analgesia not required
1	Mild	1	Mild pain. No opioid use
2		2	Moderate pain. Occasional opioid use
3		3	Severe pain. Daily opioid use
4	Moderate	**ECOG STATUS**	
5		0	Asymptomatic. Fully active, able to carry on all activities without restriction
6		1	Symptomatic. Restricted in physically strenuous activity. Able to carry out work of a light or sedentary nature
7	Severe	2	Symptomatic. <50 % in bed during the day. Ambulatory and cupable of all self-care. Unable to carry out any work activities
8		3	Symptomatic. >50 % in bed. Capable of only limited self-care, confined to bed or chair 50 % or more of waking hours
9		4	Bedbound
10	Worst	5	Death

Evaluation of Toxicity

Safety was assessed on the basis of adverse events, both hematologic, in the clinical laboratory, and gastrointestinal, in physical examination findings. All adverse events that occurred after randomization, within 3mo after the last injection of 223Ra, were reported and evaluated for their potential relationship to the study drug. Only patients with WHO's grade of 3-4 from the initial cycle of 223Ra to 3mo after the last administered dose were classified as having hematologic toxicity (ht) (Table-2).

Statistical analysis

Patient and clinical characteristics were summarized using descriptive statistics.

Median and range or 95% confidence interval for quantitative variables and categorical variables are shown as number (%). Kaplan-Meier estimates were produced for the cumulative incidence of OS, according to number of cycles of 223Ra, ECOG, basal level of Hb, metastatic involvement in bone bone-scintigraphy, and start of 223Ra-therapy. All statistical analyses were performed using SPSS for Windows.

RESULTS

Patients had a median age of 72years (range=39-88) and received a total of 183 cycles of 223Ra with a median follow-up time of 11mo (range=1.3-41).

25/40p (63%) received the 6 cycles of 223Ra, 1p (2%) received 5 cycles, and 14p (35%) received 4 cycles or less. Out of the 14p who received 4 cycles or less, 1p discontinued the treatment due to unalleviated pain, 1p due to progression, 2p died, 3p for comorbidities, 4p continued the treatment at another hospital and 3p suspended treatment due administrative problems. In Table-3, the baseline demographic and clinical characteristics of the 40p are described. Of the 26p who finished the treatment, 21p (81%) had a reduction in skeletal pain, the ECOG improved in 9p (35%), and 14p (54%) had a reduction in analgesic requirements (Figure-1).

Median value of baseline ALP in our cohort was 210.5U/L- (range=53-2370.8). We found a decrease in serum ALP level in 23/26p (88.5%), 17p with a reduction of >25% and 6p <25%, while 3p had an increase (2p >25% and 1p <25%) (Figure-2). The average reduction was 42.2%- (SD 28.1). Changes in ALP may be a useful marker for monitoring treatment with 223Ra. Further, the ALP baseline level was associated with decrease of OS.

PSA was recorded prior to the first and final cycle and the median PSA showed an upward trend of 93.55ng/mL at the beginning and 142.16ng/mL at the end.

Median OS was 17.1mo- (range=1.2-41.1, CI 95% 6.5-27.7) (Figure-3A), Median follow-up was 11.2mo- (range=1.3-45.2). 26/40p received complete treatments of 223Ra without reaching a median OS, and 14p received incomplete treatments with a median OS of 13.6mo-(CI 95% 1.6-25.6) (Figure-3B). PFS was 9.8mo- (CI95%6.6-13). 26p with complete treatments were 11.1mo (CI 95% 8.5-13.8), while those 14p with incomplete treatments were 5mo- (CI95% 2.8-7.3). TTP was 7.1mo- (CI 95% 3.9-10.3).

The univariate analysis showed that the baseline clinical variables, such as ECOG, Hb, bone-scintigraphy, ALP, and PSA, were independently associated with OS (Figures 3 C-E). Patients

Table 2 - Hematologic toxicity (according to WHO criteria).

	Hb (g/dL)	ANC (/mm3)	Platelets (/mm^3)
1	>10.0	>1,500	>75,000
2	8.0 to<10.0	1,000 to<1,500	50,000 to<75,000
3	<8.0 (transfusion indicated)	500 to<1,000	25,000 to<50,000
4	Life-threatening; urgent intervention indicated	<500	<25,000

Table 3 - Baseline patients' characteristics.

Baseline variable		n (%) /Value	Range
Age	**Mean**	**71**	**39 – 88 years**
ECOG status	Mean	1.92	1-4
	1	8 (20%)	
	2	23 (58%)	
	3	9 (22%)	
CPL	1	11 (27%)	
	2	6 (15%)	
	3	23 (58%)	
VAS	Mild (1-3)	13 (32.5%)	
	Moderade (4-6)	10 (25%)	
	Severe (7-9)	13 (32.5%)	
	Maximum (10)	4 (10%)	
Bone metastases (Bone-Scan)	2 - 6	13 (32%)	
	>6	21 (53%)	
	Superscan	6 (15%)	
Hb	Median	12.8	9.2-16.9
	<13	23 (57.5%)	
	>13	17 (42.5%)	
PSA	Median	93.5	0.26-24784
	0-20	8 (20%)	
	21-99	15 (37%)	
	>100	17 (43%)	
ALP	Median	220	53-2370
	≥200	19 (47%)	
	<200	21 (53%)	
Previous systemic treatments	Abiraterone	16 (40%)	
	Enzalutamide	3 (7%)	
	Chemotherapy	8 (20%)	
	Previous Bone Radiotherapy	19 (47%)	

Figure 1 - Trend in VAS from the 1st to the 6th^{223}Ra cycles. There is a decrease in pain during complete therapy. The main pain improvement is visualized during the first three cycles of treatment.

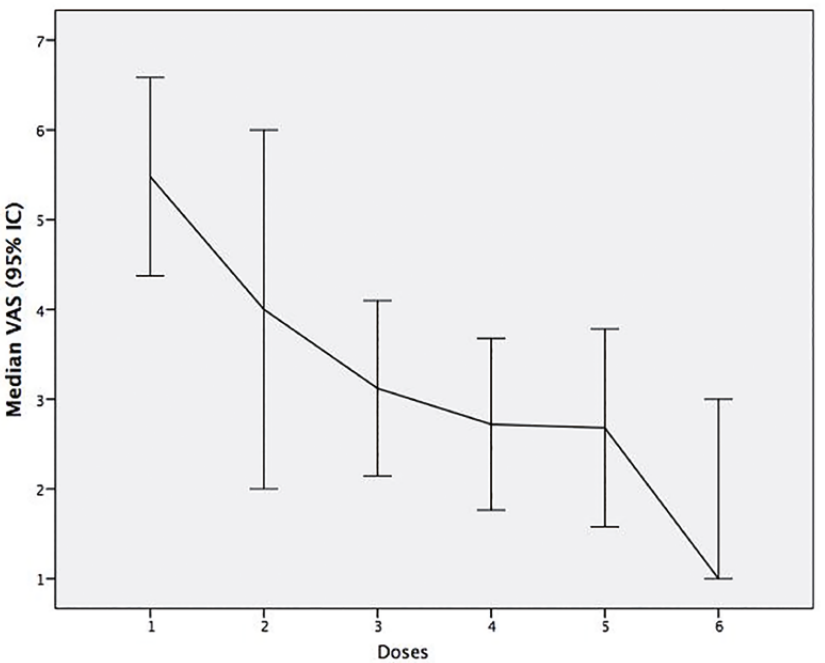


Figure 2 - Comparison ALP measurements before and after therapy with ^{223}Ra.

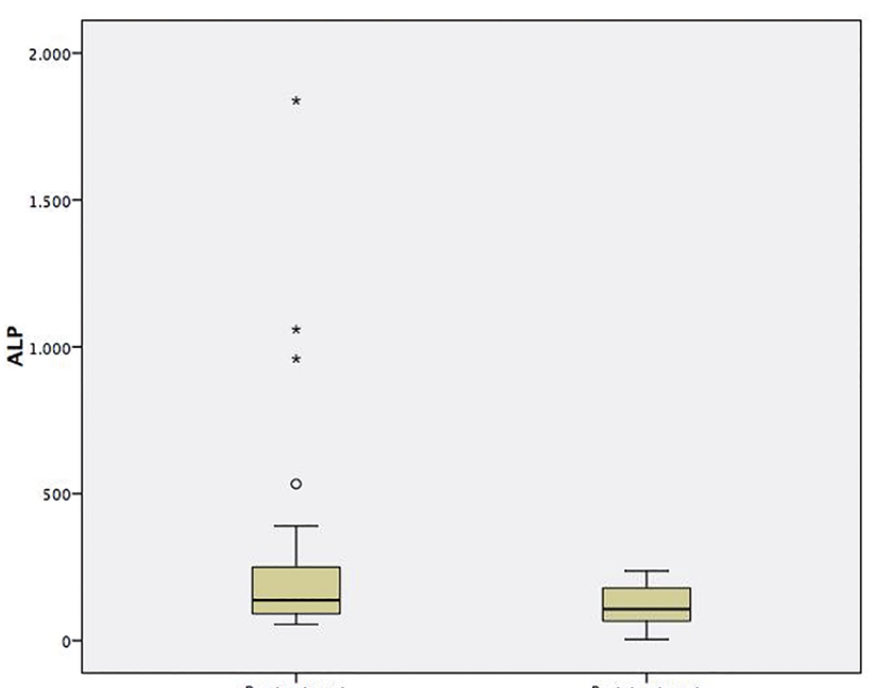
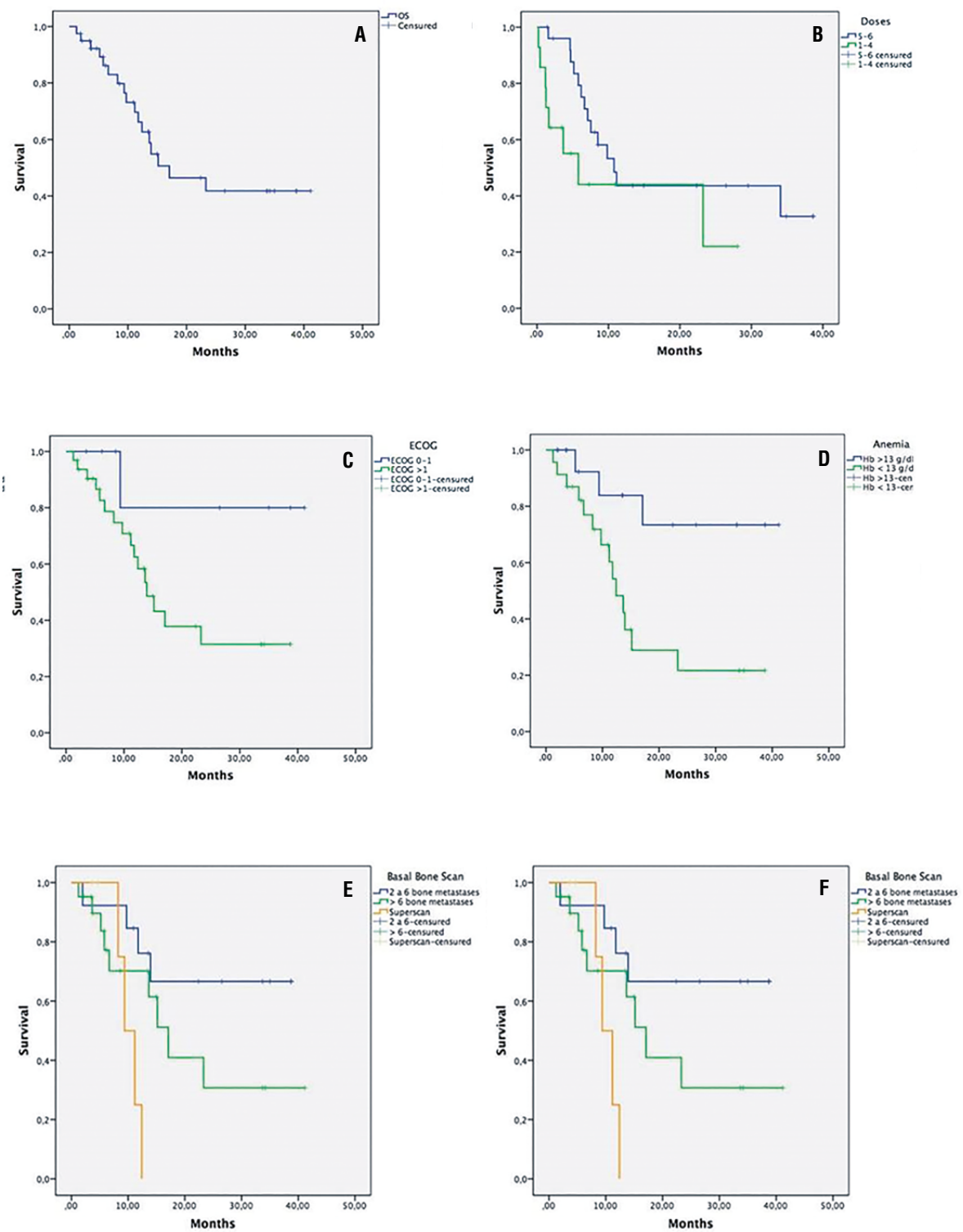


Figure 3 - Kaplan-Meier estimate showing the overall survival in our cohort according to different variables. A. Overall survival. B. Number of doses of ^{223}Ra. C. ECOG performance status. D. Basal level Hb. E. Metastatic involvement in bone scan. F. Start of ^{223}Ra therapy.



with ECOG >1, baseline Hb levels <13g/dL, superscan on bone-scintigraphy, baseline ALP levels >200U/L, and baseline PSA levels >100ng/mL were associated with an increased risk of death. 11/40p started therapy with 223Ra as the first line without reaching a median OS, while19 had been heavily pre-treated, receiving 223Ra later, with a median OS of 12.4mo, and 13 received treatment concomitant with other therapies (10p: abiraterone and 3p: enzalutamide; 6/13p: bisphosphonates) with a median OS of 13.6mo (Figure-3F). 8/40p (20%) were treated with biphosphonates before starting 223Ra, and 15/40p (37%) received concomitant treatment. Results of univariable analysis of OS are shown in Table-4.

Hematologic and gastrointestinal adverse events occurred in 57% and 42% respectively (Table-5). Ht occurred in 7/40p (18%). In 5p it

Table 4 - Univariate analysis of OS in relation to baseline variables.

Variable			Patients (n=40) n (%)	OS	
				Median	CI95%
ECOG	0-1		8 (20)	Not reached	
	>1		32 (80)	14	10.2-17.6
Hb	>13 g/dL		17 (42)	Not reached	
	<12.9 g/dL		23 (58)	12.4	9.2-15.5
PSA	0-20 ng/mL		8 (20)	Not reached	
	21-99 ng/mL		14 (35)	15.2	10.6-19.7
	>100 ng/mL		18 (45)	12.4	7.6-17.2
ALP	Missing data		1(2)		
	<200 U/L		19 (48)	Not reached	
	>200 U/L		20 (50)	12.4	7.5-17.3
Bone-Scan	2 a 6		13 (32)	Not reached	
	>6		21 (53)	17.1	12.3-21.9
	Superscan		6 (15)	9.4	6.5-12.2
^{223}Ra Therapy	First line		11 (27)	Not reached	
	Heavily pre-treated before	**Total**	19 (47)	12.4	8.1-16.7
		Abiraterone	10 (25)	9.7	6-13.5
		Enzalutamide	1 (2)		
		Chemotherapy	2 (5)		
		Chemotherapy + abiraterone	4 (10)	15.2	0.1-32.4
		Chemotherapy + enzalutamide + abiraterone	2 (5)		
	Treatment concomitant		13 (32)	13.6	7.8-19.5

Table 5 - Adverse events graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

p	Doses	Hematologic adverse event (Grades)						Gastrointestinal adverse event (Grades)					
		Anemia		Neutropenia		Thrombocytopenia		Nausea		Vomit		Diarrhea	
		1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4
1	4												
2	2	X		X									
3	2	X		X		X		X		X			
4	6	X											
5	6			X				X				X	
6	6	X			X	X							
7	6			X									
8	6	X											
9	6			X									
10	6	X		X				X		X		X	
11	6		X						X		X		
12	3												
13	6			X				X		X		X	
14	6			X				X				X	
15	6			X									
16	6	X						X		X			
17	6		X		X			X		X			
18	2	X						X					
19	6			X				X					
20	6												
21	6	X		X									
22	2	X						X		X			
23	6	X		X		X							
24	3	X											
25	6												
26	6	X						X					
27	6		X	X		X							
28	2												
29	2			X									
30	4		X	X		X		X				X	
31	6	X						X					
32	6					X		X					
33	1	X		X									
34	6	X		X		X		X					
35	5			X									
36	6												
37	4	X										X	
38	3		X	X		X		X		X			
39	6	X		X		X						X	
40	1												

was grade 3 (4p=anemia and 1p=neutropenia) and in 2p it was grade 4 (1p=anemia and neutropenia and 1p=anemia). Of the 7p who developed Ht, 3 received treatments before their 223Ra cycles (1p=chemotherapy and EBRT, 1p=abiraterone and EBRT and 1p=EBRT) and 2p received concurrent abiraterone during 223Ra treatment. 19/40p developed gastrointestinal symptoms, nausea being the most significant in 17p (89%).

DISCUSSION

Over the last years, the treatment for mCRPC has evolved considerably due to the introduction of new therapeutic agents (cabazitaxel/enzalutamide/abiraterone/223Ra). However, the main challenge, finding the best therapeutic sequencing, remains, and it could have a significant impact in terms of clinical improvement and survival. When managing mCRPC patients, many of the bone-related parameters frequently used to determine outcome denote dismal prospects for survival, and so determining which patients will benefit from therapy, in terms of OS, PFS, bone marrow depletion, and SREs, is more difficult (13, 14). As a result, there is a need to identify factors that will predict outcome, especially for new therapies, like 223Ra. The aim of this study was to evaluate in a clinical reality the role of baseline clinical variables (ECOG/ALP/Hb/number of bone metastases, and previous treatments) associated with the OS and toxicity of 223Ra-therapy, whose purpose is to identify factors that may predict a better response to treatment and provide information on the most appropriate time for the application of 223Ra. A interdisciplinary approach facilitates identification of patients who are suitable for 223Ra treatment. It has been established that the effectiveness of the treatment on survival is obtained after at least five administrations of 223Ra (15). For this reason, in this study, complete treatment for patients was defined as 5-6 cycles.

The results of this study are consistent with the findings reported in the ALSYMPCA (7), confirming that treatment with 223Ra leads to an improvement in pain rate and QoL, which was evaluated with EQ-5D-5L-score and will be reviewed later in a specific publication. Different analyses demonstrated that this treatment is well--tolerated, with a modest objective response rate, and effective in reducing ALP levels, with a clinical benefit and a positive effect on OS (16-18). Our results showed that the response to 223Ra was first clinical and later biochemical, with a moderate decrease in ALP. Taking into consideration some experiences in the literature, we evaluated the variations of ALP to assess the effect of 223Ra treatment (19-21). We observed a significant impact of 223Ra, reducing serum ALP levels by 88.5%, and we noted that the majority of these variations were associated with better pain control, decreased opioid consumption, and better functional status.

In mCRPC patients treated with 223Ra, several baseline prognostic markers associated with OS have been proposed, such as ECOG, ALP and Hb values, and prior systemic treatments. In Table-6, we describe the baseline clinical characteristics of the patients who received Ra 223 in the three different lines of therapy. Nonetheless, currently, no predictive clinical variable assessing the therapeutic benefit of 223Ra has been identified (13). The univariate analysis showed that factors like ECOG, VAS, Hb and ALP values were independently associated with OS. Decreased survival rates were seen in patients with basal Hb <13g/dL, superscan on bone-scintigraphy, PSA >100ng/mL, ALP >200U/l, ECOG >1, and those who did not finish the treatment. The use of 223Ra as the first line of therapy showed a greater OS, which suggests that early treatment is beneficial. However, due to the limited number in our sample, we were unable to draw definitive conclusions.

Elba Etchebehere et al. reported a significant benefit in the use of abiraterone concomitant to 223Ra in terms of OS, PFS, and BeFs (univariable: $p < 0.002$ and multivariable: $p < 0.044$). The use of abiraterone with 223Ra reduced the risk of death and SREs by 77% and the risk of progression by 68% (22). However, a recent analysis from the ERA-223 trial (23) showed that the simultaneous initiation of the three agents (abiraterone+prednisone/prednisolone with 223Ra) led to an increased risk of fractures and deaths. In our study, in patients who received a concomitance of 223Ra plus abiraterone (10p), OS was lowest, with a median of

Table 6 - Patients´ baseline characteristics of treated with 223Ra in the 3 lines of therapy.

^{223}Ra therapy		First line (11p)	Concomitant (Abiraterone/Enzalutamide) (13p)	Followed by other treatments (19p)
Baseline variable		n	n	n
Age	Mean	70 years	71 years	71 years
ECOG status	1	3	2	3
	≥2	8	11	16
CPL	1-2	8	2	8
	3	3	11	11
Bone metastases (Bone-Scan)	2-6	6	4	5
	>6	5	7	10
	Superscan	0	2	4
Hb (g/dL)	<12.9	4	10	11
	>13	7	3	8
PSA (ng/mL)	<99.9	10	7	7
	>100	1	6	12
ALP (U/L)	<199.9	6	5	12
	>200	5	8	7

13.6mo, without significant changes in the presence of SREs. 16/19p heavily pre-treated had received abiraterone and within this group, the majority had the most unfavorable baseline characteristics, such as Hb <13g/dL, PSA >100ng/mL, ECOG >2, CPL=3, and greater bone compromise, resulting in lower OS (Table-4). Anemia was the most frequent side effect associated with 223Ra (24, 25). In the present study, treatment with 223Ra was well-tolerated with only 7.5% of patients experiencing severe anemia (grade 4). The toxicity was manageable and reversible in most cases. The limitations of this study can be attributed to a limited number of patients, heterogeneity of the population and patient's socio-economic history, considering that some had delays in the administration of the cycles or were changed from hospital. In fact, longer time frames and larger sample sizes are needed to acquire more conclusive results in terms of OS and tolerance to other therapies after treatment with 223Ra. Nevertheless, our study provides valuable information from routine clinical practice in identifying patients who would benefit the most from 223Ra therapy, as well as the most appropriate time to initiate such treatment.

CONCLUSIONS

223Ra therapy demonstrates maximum efficacy in mCRPC patients who receive the full treatment. It is necessary to select suitable patients who will benefit from this therapy. Basal low Hb levels, bone marrow involvement and an altered performance status were the main factors that decreased survival in our patients. The use of 223Ra as the first line of therapy showed a higher OS, therefore, it should be considered relatively early in the course of treatment. Toxicity was manageable and reversible in most cases.

ABBREVIATIONS

223Ra = Radium-223
ANC = Absolute neutrophil count
ALP = Alkaline phosphatase

ALSYMPCA = ALpharadin in SYMptomatic Prostate CAncer
BMF = Bone marrow failure
CPL = WHO's Cancer Pain Ladder
ECOG = Eastern Cooperative Oncology Group
EBRT = External beam radiation-therapy
FDA = Food and Drug Administration
Hb = Hemoglobin
Ht = hematological toxicity
LDH = Lactate dehydrogenase
mCRCP = Metastatic castration resistant prostate cancer
OS = Overall survival
p = Patients
PC = Platelet count
PFS = Progression-free survival
PSA = Prostate specific antigen
SREs = The skeletal related events
TTP = Time to progression
VAS = Visual Analogue Scale for pain

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Overall survival prediction in metastatic castration resistant prostate cancer treated with radium-223

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COMMENT

Bone offers has a favorable environment that stimulates prostate cancer tumor growth in a vicious cycle fed by growth factors released by own osteoblasts (1).

Radium223 (Ra-223) is a radioisotope, it delivers energy radiation to prostate cancer bone metastasis leading to DNA damage. Ra-223 is the only commercially released alpha-emitter that targets osteoblastic bone metastases used for treatment of metastatic castration resistant prostate cancer (mCRPC).

The ALSYMPCA2 Phase III trial (2) compared Ra-223 efficacy versus placebo in 921 patients with mCRPC and symptomatic bone metastases. The study excluded patients with visceral metastases. Were included patients with disease progression (after or during) Docetaxel treatment or unfit to receive chemotherapy. The authors reported clear overall survival (OS) benefit in the Ra-223 arm compared to the placebo arm (14.9 months vs 11.3 months, HR =0.7 [95% CI 0.58–0.83]; P<0.001).

The concept of using Ra-223 earlier in the disease course, in asymptomatic or minimally symptomatic patients, is attractive. It would allow patients to complete all the six cycles of treatment and optimize sequencing with other life-prolonging therapies (3).

The combination of Ra-223, in the earlier stages of the disease, to a second-generation androgen blocker such as abiraterone (ERAS trial), and enzalutamide (PEACE-3 trial) has been reported. The ERAS trial revealed an increased risk of fractures in the Ra-223 arm (9%) versus the placebo group (3%); due to adverse effects and fractures, this combination was discouraged (4). The interim results of the PEACE-3 trial, presented at ASCO 2019, suggested that adding a bone protector (zoledronic acid or denosumab) could reduce the number of fractures, but the final results are still pending.

Until now, in the earlier stage of the disease, no sequencing using Ra-223, alone or in combination, has demonstrated survival benefit. The APCCC 2019 panel recommended the use of Ra-223 sometime during the treatment course in patients with symptomatic mCRPC and bone-predominant metastases with no visceral or bulky lymph node metastases" (panel consensus). To reduce bone fractures, the bone-protection therapy should be started before the use of Ra-223 (panel consensus) (5).

The published literature is vast, and there is no generally accepted method to identify patients with mCRPC who would benefit from Ra-223. Although PSA (Prostate-Specific Antigen), ALP (Alkaline Phosphatase) and lactate dehydrogenase (LDH) are established prognostic biomarkers in Mcrpc (6), they are not predictive of response to Ra-223.

In this series of cases, the authors pointed out that low hemoglobin (Hb) levels, bone marrow involvement and an altered performance status were the main factors related to decreased survival, identifying patients who would benefit from Ra-223 therapy (7).

Whether patients with normal Hb, no bone narrow involvement and with good performance status respond better to therapy or just live longer because of the lower tumor burden (lead-time bias phenomenon) is an open debate. Furthermore, no information about subsequent therapies was provided, making it difficult to drive conclusions regarding OS, the main endpoint of the study.

Despite this limitation, the authors reported a prospective case series in a Latin American population. They were able to demonstrate the safety and effectiveness of this therapy in a short time. Unfortunately, until now, despite the interesting mechanism of action, the Ra-223 position in the treatment sequence is still to be defined.

CONFLICT OF INTEREST

None declared.

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Role of miRNA-182 and miRNA-187 as potential biomarkers in prostate cancer and its correlation with the staging of prostate cancer

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ABSTRACT

Purpose: The microRNAs expression has emerged as a potential biomarker for the diagnosis and prognosis of prostate cancer. This study investigated the expression of miRNA-182 and miRNA-187 in prostate cancer patients and established a correlation between miRNA expression and staging of prostate cancer.

Materials and Methods: This prospective observational study involved patients undergoing transrectal ultrasound-guided biopsy for suspicion of prostate cancer. Pre-biopsy urine samples and prostatic core tissue samples of the patients were preserved and the miRNA-182 and miRNA-187 were studied.

Results: Sixty-three patients were included in this study, thirty-three patients were diagnosed with prostate cancer and thirty patients having benign histopathology were considered as controls. The expression of miRNA-182 was significantly increased (p=0.002) and miRNA-187 significantly decreased (p <0.001) in prostate cancer tissue specimens. However, the expression of these miRNAs did not significantly differ in the urine of prostate cancer patients as compared to controls. Serum Prostatic Specific Antigen (PSA) inversely correlated with the median expression of miR-187 in prostatic tissue (p=0.002). Further, the expression of miRNA-187 in prostate cancer tissue was significantly decreased in metastatic prostate cancer (p=0.037). Using ROC analysis, miRNA-187 expression was able to distinguish the presence or absence of bone metastasis [area under ROC (AUROC) (±SD) was 0.873±0.061, p <0.001].

Conclusion: The miRNA-182 and miRNA-187 appear to be promising biomarkers in prostate cancer and miRNA-187 can serve as an important diagnostic marker of metastatic prostate cancer.

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INTRODUCTION

Prostate cancer is among the common cancers of men and a major cause of cancer death. The presentation of prostate cancer may vary from an indolent disease to aggressive and metastatic disease. The current recommendations for prostate cancer screening emphasize informed decision making regarding its screening in men aged 55-69 years (1). Serum Prostate Specific Antigen (PSA) has played a key role in prostate cancer, being used not only for screening but also for the diagnosis,

prognosis, and follow-up of the treatment. Though serum PSA is widely used in clinical practice, a multitude of genomic markers has revolutionized the screening and management of prostate cancer (2). This has also led to an increased interest in the role of microRNAs (miRNAs) for the diagnosis of prostate cancer. The miRNAs are relatively small non-coding RNA molecules involved in cell development, differentiation, apoptosis, and cell proliferation. They can act as oncogenes and tumor suppressor genes, they are aberrantly expressed in human malignancies and play an important role in initiation, promotion, and metastases of these malignancies including prostate cancer (3). MicroRNA in the urine, serum and prostatic tissue has emerged as a potential biomarker for prostate cancer diagnosis and staging. However, few studies have addressed the role of miRNA as a potential biomarker in prostate cancer, thus limiting its clinical utility (4). Up-regulation of miRNA-182 and downregulation of miRNA-187 is associated with clinicopathological staging and progression of prostate cancers (5, 6). In this study, we evaluated the significance of urinary and tissue microRNAs (miRNA-182 and miRNA-187) in prostate cancer patients and their association with prostate cancer staging.

MATERIALS AND METHODS

Study design

This prospective observational study involved patients undergoing the 12-core transrectal ultrasound (TRUS) guided prostate biopsy for evaluation of prostate cancer over a period of two years. The study was approved by Institute Ethics Committee. All patients having a suspicious prostate (from digital rectal examination) or having serum PSA levels >4ng/mL underwent TRUS guided prostate biopsy. Bone scan was done in patients with histopathological proven prostate cancer.

After informed consent, the demographic profile, serum PSA and imaging findings of the patients were noted. An additional core of prostate tissue from the suspicious area was taken during the biopsy and preserved at -80°C. Urine samples of the same patients were taken in a 50mL sterile vial and preserved at -80°C before the biopsy or digital rectal examination.

Laboratory technique for expression of miRNA 182 and miRNA 187

The miRNAs were isolated from the preserved core of tissue using a mirVana RNA Isolation Kit®. The integrity of the extracted RNA pool was checked on 1X MOPS-formaldehyde agarose gel. Low molecular weight RNA was extracted using Ambion mirVana miRNA Isolation Kit® as per the manual instructions. The RNA concentration and purity were determined spectrometrically by measuring the A260/A280 ratio using the NanoDrop ND-1000 spectrophotometer (Nanodrop Technologies). RNA samples were stored at -80°C until further use.

The details of PCR primers for miRNA 182 and miRNA187 have been provided in Supplementary Table-1. miRNAs concentrations of each sample were quantified using NanoDrop ND-1000 spectrophotometer (Nanodrop Technologies). 500ng/ul of miRNA was used as template for cDNA synthesis using Taqman microRNA Reverse transcription kit® (cat no. 4366597, Thermofisher Scientific Inc, USA).

The RNA isolation from fresh whole urine collected (50mL) involved centrifugation at 2500g, 23°C, for 15 minutes. The supernatant was then discarded and the remaining sediment was resuspended in 1mL of 1X PBS and again centrifuged at 2500g, 23°C, for 15 minutes to wash the sediments. Final pellet was used for RNA isolation with RNeasy Mini Kit® according to manufacturer's protocol (Kit, Qiagen RNeasy).

We used microRNA isolation and purification kit (Cat No. 29000) from Norgen Biotek corp, Canada. We followed manufacturer instructions. The protocol was started with 15mL urine sample of each patient and lysis was done in lysis buffer with β-mercaptoethanol and vortexed to lyse cells. Molecular grade 99.9% ethanol was then added to precipitate miRNAs and the samples were centrifuged through a kit-supplied spin column. When all material mix was passed through, the column was then washed using the supplied wash buffer, dried and the kit elution solution applied. The final RNA was eluted in 50µL volume.

Table 1 - Baseline characteristics of the study population.

Parameter	Total population (n=63)	Patients with prostate cancer (n=33)	Controls (n=30)
Mean age (±SD), years	65.3±8.0	65.2±7.8	65.3±8.5
Digital rectal examination			
Firm non nodular prostatomegaly	41 (65.1%)	11 (33.3%)	30 (100%)
Hard or nodular prostatomegaly	22 (34.9%)	22(66.7%)	-
Median PSA (IQR), ng/mL	15 (8-50)	47 (15-100)	10 (8-14)
Number of patients with PSA range, n (%)			
0-10 ng/mL	21 (33.4%)	5 (15.2%)	16 (53.3%)
10-20 ng/mL	15 (23.8%)	7 (21.2%)	8 (26.7%)
>20 ng/mL	27 (42.8%)	21 (63.6%)	6 (20%)
Histopathological Grade Group, n (%)			
Gleason Grade group 1 (GS=6)		6 (18.1%)	
Gleason Grade group 2 (GS=3+4)		2 (6.1%)	
Gleason Grade group 3 (GS=4+3)		5(15.2%)	
Gleason Grade group 4 (GS=4+4)		5 (15.2%)	
Gleason Grade group 5 (GS=9,10)		15 (45.4%)	
Metastasis on Bone scan, n (%)			
Absent		16 (48.5%)	
Present		17 (51.5%)	
Oligometastatic disease (≤4 sites)		7/17 (41.2%)	

Expression levels of the miRNAs hsa--mir-182 and hsa-mir-187 were determined by quantitative real-time PCR (BIORAD C96f Real--Time PCR machine) using TaqMan microRNA Reverse transcription kit® and SoS Eva Green qPCR Master Mixes® (Biorad®) with the designed primers (Sigma®). The primers designed used are mentioned in Supplementary Table-1. The Real--Time detection of amplified PCR products was based on the detection of fluorescent signals generated by binding of SOoS Eva Green to double--stranded DNA. The fluorescent signal from each PCR reaction was collected as the peak-normalized values plotted versus the cycle numbers. The reactions were characterized by comparing the threshold cycle (Ct) values. Ct is a unitless value defined as the fractional cycle number at which the normalized sample fluorescence signal passes a fixed threshold above baseline when it is always located within the linear phase of amplification. The samples with a high starting copy number of cDNA show an increase in fluorescence earlier in the PCR process, therefore resulting in a low Ct number. The small nuclear RNA U6 served as an internal control (RNU6B). The reactions were performed in two cyclic programs at 95°C for 30 sec, followed by 40 cycles of 95°C for 15 sec and 55°C for 30 sec. All reactions were run in duplicates.

Statistical analysis

The miRNA expression of the patients along with demographic characteristics and histopathological reports were entered in a Microsoft Excel® spreadsheet. Continuous variables were expressed as mean±standard deviation (SD) or median (Interquartile range [IQR]) as appropriate. Categorical variables were compared using the chi-square test and continuous variables were compared using Wilcoxon-rank sum test and

Kruskal-Wallis rank test as appropriate. Statistical significance was taken as p <0.05. Data were analyzed using IBM SPSS Statistics® software (version 20.0, Chicago. IL, USA).

RESULTS

63 patients were included in the study. 33 patients were diagnosed with prostate cancer while the remaining 30, having no evidence of malignancy in TRUS guided biopsy, were included as controls. The baseline characteristics of the study population are presented in Table-1.

Expression of miRNA

Two microRNAs, miR-182 and miR-187, were studied and their expression was analyzed in both tissue and urine samples. The expression of miR-182 was significantly higher (p=0.002) and miR-187 was significantly lower (p=0.001) in prostate cancer tissues as compared to controls. A similar trend was seen in urine samples but it did not reach the statistical significance level [miR-182: p=0.879 and miR-187: p=0.201). Table-2 describes the detailed expression of the various miRNA in the two groups.

Relationship of miRNA with PSA, grade, and metastasis in prostate cancer

The patients were grouped into 3 groups based on serum PSA levels: 0-10ng/mL, 10-20ng/mL and >20ng/mL. The miRNA expressions between the various groups were compared using Kruskal-Wallis test. The miRNA expression varied inversely with increasing PSA risk category (p=0.002). However, no other significant association was observed between miRNAs expression in prostatic tissue or urine and serum PSA levels (Table-3).

Patients were divided into groups based on Gleason's score on histopathology. Group 1 included Gleason Score <6, Group 2 included Gleason Score 3+4=7, Gleason Group 3 included Gleason Score 4+3=7, Gleason Group 4 included Gleason Score 4+4=8 and Gleason Group 5 included Gleason Score 9 or 10. The mi RNA 182 and 187 expressions did not vary significantly between these groups, based on the Kruskal-Wallis test, as shown in Table-3. Similarly, miRNA expressions did not vary significantly between various classes of D'Amico risk stratification of prostate cancer.

Bone scan was done on patients with prostate cancer. 17 patients had metastases whi-

Table 2 - Median expression of miRNA-182 and miRNA-187 in patients with prostate cancer and controls.

Sample	miRNA	Prostate cancer (n=33)	Control (n=30)	p- value
Prostatic tissue	miRNA-182	4.99 (1.36, 7.58)	3.17 (0.10, 8.34)	0.002*
Prostatic tissue	miRNA-187	1.67 (1.31, 2.28)	4.60(.11, 10.51)	<0.001*
Urine	miRNA-182	4.35 (1.06, 9.89)	3.81 (.20, 7.7)	0.200
Urine	miRNA=187	1.87 (.31, 7.04)	2.11 (.10, 4.86)	0.879

Table 3 - Correlation of miRNA expression with various aspects of prostate cancer (n=33).

Parameter	Tissue miRNA-182 expression	Tissue miRNA-187 expression	Urinary miRNA-182 expression	Urinary miRNA- 187 expression
Serum PSA	0.953	**0.002***	0.678	0.157
Gleason Grade group	0.841	0.567	0.879	0.721
D'Amico Risk stratification	0.547	0.066	0.547	0.212
Metastasis on bone scan	0.130	**<0.001***	0.800	0.879

PSA = Prostate Specific Antigen; p-value calculated using Wilcoxon-rank sum test or Kruskal-Wallis test as appropriate; * p<0.05 considered as significant

le 16 patients did not have metastasis. The expression of miR-187 was significantly decreased in prostate biopsy of metastatic prostate cancer patients (p <0.001, Kruskal Wallis test). However, there was no significant difference between miR-182 expression in prostatic biopsy tissues and miRNA expression in urine with metastases. Figure-1 depicts the correlation of expression of various miRNAs with the presence or absence of metastases.

Using ROC analysis to study the utility of miR-187 expression to distinguish the presence or absence of bone metastasis, area under ROC (AUROC) (±SD) was 0.873±0.061 (95% CI; 0.754-9.993, p <0.001). Using Youden's index method, the median expression of miR-187 in prostatic tissue of 2.00 had 68.8% sensitivity and 100% specificity to predict the presence of bone metastases in prostate cancer (Figure-2).

DISCUSSION

The miRNAs play an important role on cellular differentiation including the biochemical signalling of various oncogenic pathways (7, 8). The miRNAs alter the cell cycle regulation, angiogenesis, and metastasis but the deciphering the exact relation between miRNA and cancer is complex (9-11). In malignancy, the differential expression of miRNA appears to be the cause as well as the effect of oncogenesis. The miRNAs can be both oncogenic or anti-oncogenic (12-14). Thus, although the differential expression may provide diagnostic and prognostic benefit, the actual rea-

Figure 1 - Graph depicting the association between presence or absence of bone metastases with A) miRNA-187 expression in prostatic tissue; B) miRNA-182 expression in prostatic tissue; C) miRNA-187 expression in urine; D) miRNA-182 expression in urine in prostate cancer patients.

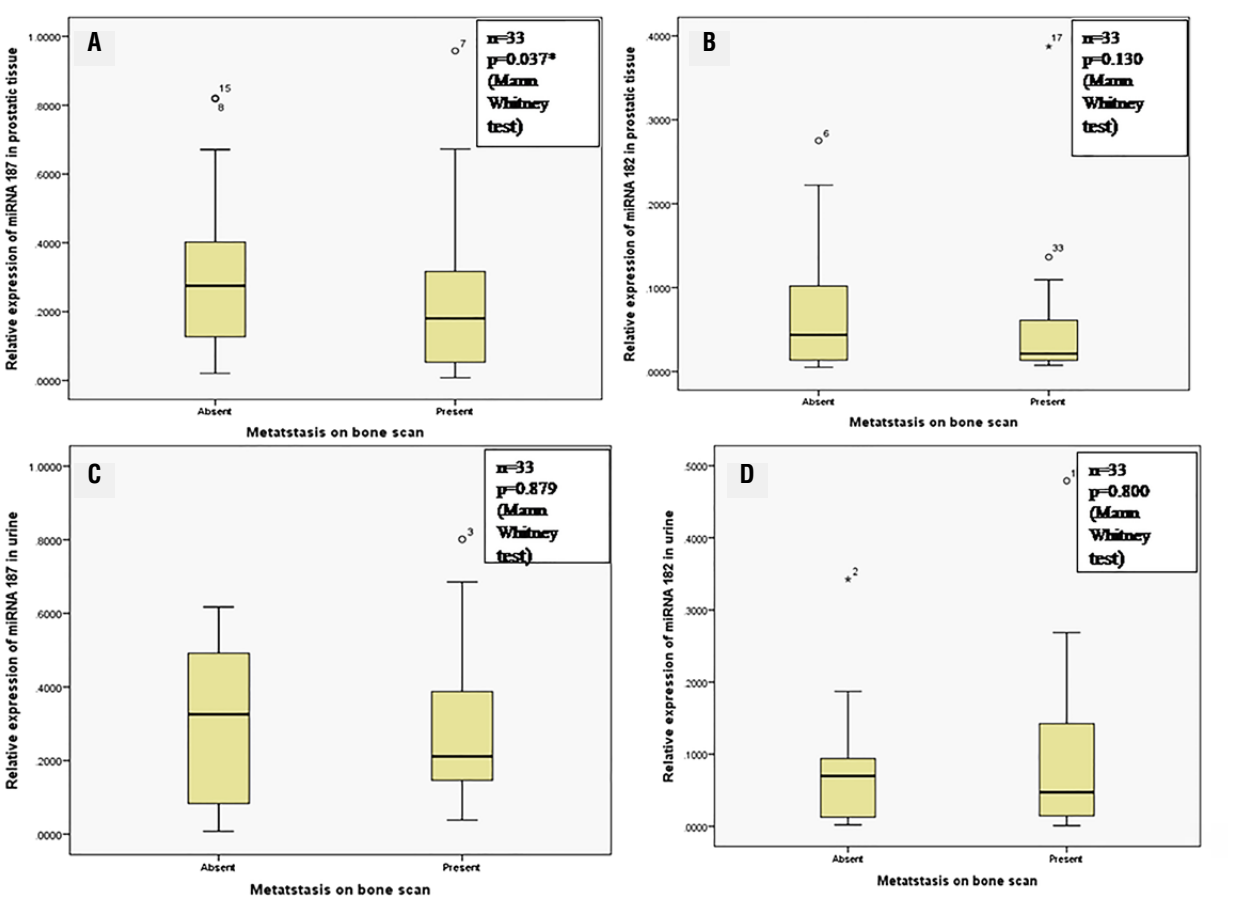
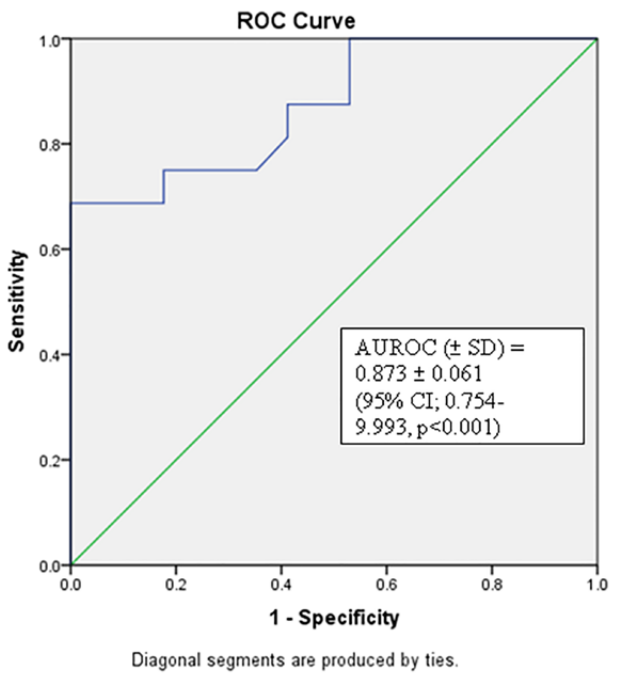


Figure 2 - Receiver operating characteristic curve of mi RNA-187 expression in prostatic tissue with presence or absence of metastasis on bone scan;



son for such a change is multi-factorial and still to be deciphered.

Over the last few years, various studies have identified miRNAs that are differentially expressed in prostate cancer. The expressions of these miRNAs have been linked to androgen signaling as well as clinic-pathological factors (15-17). Furthermore, it has been advocated that miRNAs may be new contenders for cancer drug treatment, given the oncogenic or tumor suppressive functions of miRNAs (18). Nevertheless, the results of the various studies are conflicting.

Detection of clinically significant prostate cancer and identification of the suitable candidates for active surveillance versus radical treatment forms the mainstay of management of prostate cancer. At present, PSA kinetics, tumor grade (Gleason score), and the clinical stage classify the prostate cancer patients. Even though these factors are clinically beneficial, they have limitations in identifying cases, predicting disease outcomes and controlling clinical management decisions (19-21). Thus, new biomarkers are needed to improve existing diagnostic, prognostic and treatment management strategies.

We investigated the abnormal expression of miRNAs based on expression signatures in prostate cancer. Upregulation of miR-182 was formerly described in prostate cancer and other tumors, while miR-187 was later found to be lost in prostate cancer and ovarian carcinoma but overexpressed in breast cancer progression (22-25).

In this study, we found the upregulation of miR-182 and downregulation of miR-187 in prostate cancer. Similar results were reported by Casanova-Salas et al. (26). Furthermore, miR-182 and miR-187 were also differentially expressed according to clinical variables, such as the tumor stage, Gleason score, the status of TMPRSS2-ERG and progression. Fuse et al. (22) also reported the downregulation of miR-187 along with miR-224, 34 and 221 in prostate cancer.

In another study by Schaefer et al., (24) the miRNA expression was correlated with histopathological grade and clinical stage of prostate cancer. They identified ten microRNAs including hsa-miR-16, hsa-miR-31 etc being downregulated while 5 miRNAs including hsa-miR-182 upregulated in prostate cancer. The expression of upregulated miRNAs correlated significantly with tumor stage and grade. Moreover, two microRNAs classified up to 84% of malignant and non-malignant samples correctly. This highlighted the role of differential expression of miRNA as diagnostic and prognostic marker of prostate cancer. However, in another study by Tsuchiyama et al., (27), the expression of various miRNAs did not vary significantly among various Gleason patterns.

In this study, we did not find any statistically significant association between miR-182 expression and clinical-pathological parameters. However, we found an association between miR-187 expression and metastatic prostate cancer. We also report the role of miR-187 in diagnostic utility to differentiate the presence or absence of metastases with AUROC of 0.873 ($\pm$0.061).

Moreover, miRNA expression assessment in extracellular body fluids such as plasma, serum, saliva or urine may provide a benefit in can-

cer diagnosis, detection of progression and recurrence of prostate cancer. The feasibility of urine-based testing in prostate cancer has previously been documented in some studies (4).

Casanova-Salas et al. (28) studied 92 patients of prostate cancer undergoing needle biopsy, and proposed a prediction model involving miR-187, urine PCA3 and serum PSA with a sensitivity of 88.6% and specificity of 50% specificity and 69.3% diagnostic precision, which was significantly higher than PSA alone. Srivastava et al. (29) evaluated the expression of 8 miRNAs in urine and tissue samples of prostate cancer. miR-205 and miR-214 were significantly downregulated in prostate cancer patients in both tissue and urine specimens. This miRNA profile was reported to distinguish patients of prostate cancer from healthy individuals with a sensitivity of 89% and a specificity of 80%. Baumann et al. (30) studied mi-RNA 182 expression using in situ hybridization of two prostatic tissue microarrays and reported significantly higher mi-RNA 182 expression in cancer epithelium as compared to adjacent benign epithelium. However, ratio of miR-182 expression in cancer vs benign cells per patient was inversely associated with recurrence in a multivariate logistic regression model.

Haj-Ahmad et al. (31) performed miRNA expression profiling in urine samples of healthy males, BPH patients and prostate cancer patients using whole genome expression analysis. They found that the differential expression of two individual miRNAs (miR-1825 and -484) between healthy people and BPH patients was identified and found to possibly target genes related to prostate cancer development and progression among 894 miRNAs assayed. This study evaluated the expression of miRNA in urine but did not find any significant difference in prostate cancer patients.

This study has several strengths. It was a prospective study including patients with prostate cancer and the controls with a similar demographic profile. The histopathology was studied by a single genital-urinary pathologist and the expression of miRNA was done in a standardized manner. Both urine sample and tissue samples were used to study the expression of miRNA. Using ROC analysis, miR-187 appeared to have a role to distinguish the presence or absence of bone metastasis in carcinoma prostate.

However, there are certain limitations in this study. Firstly, we selected the pre-identified miRNA for this study and did not perform microarray analysis for identification of all dysregulated miRNAs. Secondly, the limited sample size may be a possible explanation for the lack of correlation between miRNA expression and clinical-pathological features. Thirdly, the lack of statistical findings might be due to unsampled tumor in the control group, especially since MRI was not performed. Fourthly, the inverse relationship between miR-187 and PSA is likely due to the fact that miR-187 tracks with cancer, not that it tracks independently with PSA. While miRNA-182 and 187 are biomarkers, they may not necessarily convey obvious function. Lastly, we did not analyze the miRNAs in serum which could have been an additional marker for prostate cancer diagnosis. Metastasis work-up using Ga-PSMA PET scan would have been a better modality as compared to the bone scan. However, in a resource-limited setup, PSMA PET was not feasible for all patients.

CONCLUSIONS

The microRNA expression is a potential tool to improve existing diagnostic, prognostic and treatment strategies for prostate cancer. The miRNA-182 and miRNA-187 appear as important biomarkers in prostate cancer, and miRNA-187 may be used to increase the diagnostic and prognostic accuracy in the management of prostate cancer.

DISCLOSURE

The abstract of this research work titled as 'The miRNA-182 and miRNA-187 as potential biomarkers in prostate cancer patients' was presented on 36th World Congress of Endo-urology at Paris, France from 20th September, 2019 to 24th September, 2019
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CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplementary Table 1 - Details of primer sequence of miRNA-182 and miRNA 187 used for reverse transcriptase reaction.

Name of miRNA	Sequence (5'-3') of primer
miRNA-182	ACTTTTGGCAATGGTAGAACTCAC
	GTGCAGGGTCCGAGGT
miRNA-187	TCGTGTCTTGTGTTGCAGC
	GTGCAGGGTCCGAGGT

ORIGINAL ARTICLE

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Stress Urinary Incontinence post-Holmium Laser Enucleation of the Prostate: a Single-Surgeon Experience

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ABSTRACT

Purpose: To identify incidence and predictors of stress urinary incontinence (SUI) following Holmium laser enucleation of the prostate (HoLEP).

Materials and Methods: We performed a retrospective review of 589 HoLEP patients from 2012-2018. Patients were assessed at pre-operative and post-operative visits. Univariate and multivariate regression analyses were performed to identify predictors of SUI.

Results: 52/589 patients (8.8%) developed transient SUI, while 9/589 (1.5%) developed long-term SUI. tSUI resolved for 46 patients (88.5%) within the first six weeks and in 6 patients (11.5%) between 6 weeks to 3 months. Long-term SUI patients required intervention, achieving continence at 16.4 months on average, 44 men (70.9%) with incontinence were catheter dependent preoperatively. Mean prostatic volume was 148.7mL in tSUI patients, 111.6mL in long-term SUI, and 87.9mL in others (p <0.0001). On univariate analysis, laser energy used (p <0.0001), laser "on" time (p=0.0204), resected prostate weight (p <0.0001), overall International Prostate Symptom Score (IPSS) (p=0.0005), and IPSS QOL (p=0.02) were associated with SUI. On multivariate analysis, resected prostate weight was predictive of any SUI and tSUI, with no risk factors identified for long-term SUI.

Conclusion: Post-HoLEP SUI occurs in ~10% of patients, with 1.5% continuing beyond six months. Most patients with tSUI recover within the first six weeks. Prostate size >100g and catheter dependency are associated with increased risk tSUI. Larger prostate volume is an independent predictor of any SUI, and tSUI.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common condition affecting many older men. In the United States, more than 70% of men aged 60-69 years have symptoms associated with BPH. Currently, lower urinary tract symptoms (LUTS) impact almost 80% of men older than 70 (1).

Historically, transurethral resection of the prostate (TURP) has been the gold standard for endoscopic management of BPH (2). This technique, although effective, has many potential adverse effects and limitations which have prompted the advent of newer treatment modalities for BPH (3-5). Holmium-laser enucleation of the prostate (HoLEP) is one of the most prominent newer modalities. HoLEP is size independent and can be

used for enucleation of prostates over 100g, which has traditionally been a limitation of TURP. Recent studies have shown that HoLEP is equally as effective, and potentially more effective, when compared to TURP and open simple prostatectomy across a variety of outcomes (4).

With HoLEP now recognized in the AUA guidelines as a viable alternative treatment option for those with moderate to severe LUTS, it is important to understand better the adverse event profile associated with this procedure (6). In our institutional experience, the most common complication encountered with HoLEP is postoperative stress urinary incontinence (SUI). The vast majority of SUI seen after HoLEP is transient, with the majority of cases resolving within one year (7). We have found that transient SUI (tSUI) represents one of the most common complaints affecting patient satisfaction and the quality of life postoperatively. Recent reports note that the rates of postoperative SUI range between 1.4% and 44% following HoLEP (8-11). The wide range in reported SUI rates is most likely multifactorial and may be due to different operative techniques, surgeon experience, and patient-specific factors. Unfortunately, many of these studies are limited by small sample sizes and technique heterogeneity.

With this study, we aim to more accurately define SUI rates using a large single-surgeon single-institutional experience and to identify the incidence and predictors of SUI following HoLEP. With this knowledge, surgeons can better counsel patients regarding the procedure allowing for more informed patient decision making and improve patient satisfaction.

MATERIALS AND METHODS

We performed an IRB approved (Control #12D.50) retrospective chart review of all patients undergoing HoLEP at our institution between January 2012 and June 2018. Our review included the charts of all patient who underwent HoLEP at our institution within this time period under the care of a single surgeon. The exclusion criteria for this review include incomplete surgical resection and lack of post-operative follow-up. Baseline demographic data collected included age, body mass index (BMI), serum prostate-specific antigen (PSA), prostate volume, peak Uroflow rate, mean Uroflow rate, PVR volume, IPSS score, and IPSS QOL rating. All patients underwent urodynamic testing (Laborie Medical Technologies®) before undergoing surgery to confirm the diagnosis of bladder outlet obstruction. All procedures were performed by a single experienced surgeon (A.D.) who had performed more than one thousand HoLEP cases before the study period. Postoperative clinic visits were conducted within two weeks, at six weeks, and at three months. Assessment at postoperative visits included the IPSS questionnaire, PVR, and Uroflow testing.

Our trilobar HoLEP technique has been described previously, but in brief, a 26 French (Fr) continuous flow resectoscope with a laser bridge adapter and an endoscopic camera are utilized (12). The laser fiber is passed through a 6Fr open-ended ureteral catheter. A 100 Watt holmium laser with an end-firing 550-micron laser fiber is used with energy settings of 2.0J and 50Hz. After trilobar enucleation is completed, a morcellator, grasper, or both are used to clear the bladder of any prostatic tissue.

At postoperative visits, SUI was assessed clinically, which was defined as incontinence during activity with a patient-reported negative impact on quality of life. Any patient who reported incontinence which necessitated the utilization of undergarment pads or diapers was considered "incontinence", while those who did not report needing any pads or diapers were considered continent for our study purposes. SUI was differentiated from other forms of incontinence by careful history taking and physical examination in the clinic. Patients with different types of incontinence, such as urge or mixed, were excluded from this study. For study purposes, SUI was considered transient if it resolved within six months of the procedure date, in following with previous literature (6). Any leakage beyond six months was deemed to be long-term SUI.

Additional risk factors assessed included prostate size as measured by TRUS, CT, or MRI imaging. Patients were risk stratified based on preoperative prostate size (>100g or ≤100g) and pre-operative catheter dependency status (clean intermittent catheterization and continuous urethral drainage).

Univariate analysis for baseline demographics and perioperative risk factors were completed using the chi-square test for categorical variables and ANOVA for comparison of continuous variables. Multivariable logistic regression was completed to identify factors predictive of increased risk for any SUI, transient SUI, and long-term SUI after HoLEP. Significant factors from the univariate analysis were included in the multivariable analysis. Analyses were completed using SPSS®, version 23.0.

RESULTS

Five hundred eighty nine men undergoing HoLEP during the study period were identified. Postoperative tSUI occurred in 52 men (8.8%), while 9 (1.5%) had long-term SUI, for a total of 61 (10.4%) patients who experienced any SUI after HoLEP. Of the patients who experienced tSUI, all had their incontinence resolved within three months. 46 men (88.5%) with tSUI had full resolution of incontinence within the first six weeks, while the remaining 6 men (11.5%) resolved between six weeks and three months.

Table-1 highlights preoperative baseline characteristics as well as perioperative results. Except for pre-operative prostate size (tSUI: 148.7±56.8mL, long-term SUI: 98.0±50.1mL, no SUI: 92.2±50.6mL, p <0.0001),

Table 1 - Baseline Characteristics, Preoperative, and Perioperative Data.

	Patients with no SUI (n=528)	tSUI patients (n=52)	Long-term SUI (n=9)	p-value
Preoperative Data				
Age	70.6±8.5	72.0±8.9	65.6±5.7	0.1027
BMI	28.7±7.8	29.6±5.8	28.2±4.1	0.7026
Serum PSA (ng/mL)	10.03±47.45	6.7±7.4	9.0±7.1	0.9388
Prostate Size (mL)	92.2±50.6	148.7±56.8	111.6±48.5	<0.0001
Pre-Op Uroflow Peak Flow (mL/s)	8.6±9.9	14.7±23.5	11.5±10.8	0.0009
Pre-Op Uroflow Mean Flow (mL/s)	3.4±2.5	3.7±3.2	3.5±1.8	0.9367
Pre-Op Post Void Residual (mL)	238.8±249.2	297.0±298.1	185.2±112.3	0.3030
Pre-Op IPSS Results	19.7±8.5	17.9±9.8	19.4±5.8	0.5897
Pre-Op IPSS QOL Results	3.6±1.2	3.5±1.5	3.8±0.7	0.8231
Pre-operative Catheterization (N, %)	201 (38.1%)	37 (71.2%)	7 (77.8%)	<0.0001
Perioperative Data				
Laser Energy Used (kJ)	339.3±190.4	514.4±151.4	434.3±145.8	<0.0001
Laser On Time (min)	118.7±72.8	163.5±89.7	174.2±67.4	0.0204
Resected Prostate Weight (g)	70.2±42.8	135.5±70.5	103.2±52.4	<0.0001
Post-Op Catheterization Time (days)	5.5±3.5	4.9±2.1	6.6±4.6	0.6139
Post-Op Uroflow Peak Flow (mL/s)	24.3±17.6	24.0±11.6	24.8±9.5	0.9926
Post-Op Uroflow Mean Flow (mL/s)	6.4±4.8	5.1±3.2	6.4±1.7	0.6384
Post-Op Post Void Residual (mL)	63.4±89.3	63.4±78.5	10.3±10.5	0.3414
Post-Op IPSS Results	6.8±5.9	9.5±8.3	16.7±11.4	0.0005
Post-Op IPSS QOL Results	1.1±1.4	1.8±1.4	2.4±2.0	0.0214

Continuous data is presented as mean ± standard deviation; categorical data as proportions

pre-operative Qmax (tSUI: 14.7±23.5mL/s, long-term SUI: 11.5±10.8mL/s, no SUI: 8.6±9.9mL/s, p=0.0009) and pre-operative catheter dependence (tSUI: 71.2% vs. long-term SUI: 77.8% vs. no SUI: 38.1%, p <0.0001), there was no significant difference between men who developed transient SUI, long-term SUI, and those who did not.

With regard to perioperative and postoperative results, patients who developed SUI were found to have greater laser energy used (tSUI: 514.4±151.4 kJ vs. long-term SUI: 434.3±145.8 kJ vs. no SUI :339.3±190.4 kJ, p <0.0001), longer laser "on" time (tSUI: 163.5±89.7 min, long-term SUI: 174.2±67.4 min, no SUI: 118.7±72.8 min, p=0.0204), larger resected prostate weight (tSUI: 135.5±70.5g, long-term SUI: 103.2±52.4g, no SUI: 70.2±42.8g, p <0.0001), higher overall IPSS score (tSUI: 9.5±8.3, long term SUI: 16.7±11.4, no SUI: 6.8±5.9, p=0.0005) and IPSS QOL scores (tSUI: 1.8±1.4, long term SUI: 2.4±2.0, no SUI: 1.1±1.4, p=0.0214).

When patients with tSUI were stratified by preoperative prostate volume of >100g (n=44) or ≤100g (n=8), 8 men (100%) with prostates ≤100g had the resolution of tSUI within 6 weeks. In the 44 men with larger (>100g) prostates, 38 (86.3%) had the resolution of tSUI within 6 weeks, while the remaining 6 (13.6%) had the resolution between 6 weeks to 3 months. There was not a statistical significance (p=0.2394) in recovery time when comparing larger prostates (>100g) to smaller prostates (≤100g).

On multivariable logistic regression analysis, we performed multiple analyses looking for predictive factors predisposing patients to any SUI (Supplementary Table-1.1), tSUI (Supplementary Table-1.2), and long-term SUI (Supplementary Table-1.3). Results showed that only resected prostate weight was a significant predictor of developing any SUI (HR 1.020, 95% CI 1.007-1.033, p <0.05) and tSUI (HR 1.019, 95% CI 1.006-1.032, p <0.05). There were no risk factors identified for long-term SUI patients.

DISCUSSION

HoLEP has struggled to gain widespread adoption within the urology community due to a well-established steep learning curve, requiring up to 50 cases to become proficient (11, 13, 14) The potential development of tSUI has also been a limiting factor in its uptake. SUI, the involuntary leakage of urine, is distressing and has been shown to decrease the quality of life in patients (15). Patient distress likely plays a role in the avoidance of this prostate reducing technique by surgeons.

In our study, we evaluated the incidence and predictors of SUI after HoLEP. We then looked to compare our results to those of other prostate reducing procedures in the literature. In patients undergoing TURP, the incidence of long-term stress incontinence is rare (~1%), although 30-40% of patients have tSUI resolving within six months (16, 17). On the other hand, in men undergoing open simple prostatectomy (OP), there is a much higher incidence of long-term incontinence ranging between 1-40% depending on the technique utilized, with more current data showing 20.2% of patients becoming permanently incontinent (18-21). Further studies have shown a 38.6% incidence of tSUI in the three months following simple prostatectomy (22). In comparison, the incidence of long-term and transient SUI in our single-surgeon series is 1.5% and 8.8%, respectively. Our results suggest improved surgical outcomes compared to the published literature.

Both HoLEP and simple prostatectomy seek to provide complete enucleation of the adenoma. Our HoLEP technique involves endoscopic dissection of the adenoma in a retrograde fashion, from the distal to the proximal attachments. HoLEP allows for distal visualization of the adenoma, compared to the blind approach taken with OP. We feel that this visualization confers an advantage, as visual landmarks allow for the surgeon to avoid damage to the sphincter, and may play a role in lower incontinence rates seen in HoLEP versus OP.

Variable tSUI rates after HoLEP have been reported in the literature. Previous studies have outlined this complication as occurring in anywhere from 1.4-44% of patients, of which the vast majority recover full continence by one year (10, 11, 23). A more recent large cohort study from Japan reported a tSUI rate after HoLEP of 16.6%, which is more consistent with our series (8). However, while the extreme variation in reported SUI

rates postoperatively is likely a function of small sample sizes, variable operative experience, heterogeneous operative techniques, and possible prior bladder dysfunction, our series has the advantage of being a large single-surgeon series. Shah et al. assessed the amount of time required to regain bladder control following HoLEP and found that it took 42.3 days (24). These results are consistent with our study, in which all patients who developed tSUI had complete a recovery by three months. We assessed if a larger prostate size was associated with rate of tSUI recovery. All six patients who took over 6 weeks to recover had large prostate volume, while no patients took over 6 weeks with a low prostate volume. Though the analysis did not show statistical significance (p=0.2394), the absolute numbers suggest that men with larger prostate may have a slightly slower rate of recovery.

This study also sought to uncover risk factors that may predispose patients to SUI, both transient and long-term. There was a statistical difference seen amongst the three groups on analysis for preoperative prostate size, preoperative Qmax, laser "on" time, laser energy used, and resected prostate volume. A novel finding of our study was the association of preoperative catheter dependence with postoperative incontinence. The cause of this correlation remains unknown, but it is possible that patients requiring preoperative catheterization have more severe BPH, and therefore require longer endoscopic manipulation, which predisposes the patients to SUI. The only prior study looking at risk factors by Nam et al. identified increasing age and operative time as risk factors (25). However, on our multivariate logistic regression analysis, only resected prostate weight was a significant predictor of developing any SUI (HR 1.020, 95% CI 1.007-1.033, p <0.05) and tSUI (HR 1.019, 95% CI 1.006-1.032, p <0.05).

Our study showed the rate of long-term incontinence to be very low. While no preoperative risk factors predisposing patients to long-term SUI were identified on multivariate regression, post-analysis chart review of these 9 patients uncovered a high rate of neurological comorbidities. Further investigation showed that 8/9 (88.9%) patients had a significant neurological history. However, as we cannot accurately capture the incidence of neurological comorbidities that exist within the rest of the population, a comparison was not possible. Of the 8, 7 had spinal pathology, including spinal stenosis and degenerative disc disease, while 1 had myasthenia gravis. Critically, all of these patients were able to achieve either complete resolution of SUI or reduction to less than 2 pads/day. The management strategies for these patients included initial pelvic floor exercise therapy, and in those still unsatisfied, coaptite injections. Multiple coaptite injections were given to patients who had partial responses. Only one patient went on to require AUS implantation. These 9 patients achieved a satisfactory level of continence at an average of 16.4 months after the completion of their HoLEP.

When assessing postoperative QOL outcomes, we found that men with tSUI and long-term SUI had worse postoperative IPSS scores (both worse subjective symptoms and quality of life responses) when compared to those patients who did not experience tSUI. As expected, SUI had a substantial negative impact on quality of life. This result is in line with previous reports showing the quality of life impact that incontinence can have on patients (26).

One possible cause of incontinence seen after surgery is sphincter dysfunction, which is likely the result of prolonged endoscopic manipulation. Endoscopic procedures are thought to cause trauma directly to the sphincter, leading to this dysfunction. This dysfunction is thought to be temporary, causing the transient nature of the SUI (8, 11, 27) A larger prostate size leads to longer operative times, which may explain the correlation between tSUI and both larger prostates and longer operative times. The longer laser time and laser energy used, as well as the heavier weight of resected prostate tissue, are all associated with a larger prostate. All of our results seem to indicate that larger prostates cause longer operations, and therefore increased endoscopic manipulation and risk for tSUI via sphincter dysfunction. As many of the variables associated with tSUI on univariate analysis were surrogate markers of prostate size, this may explain why

they were not independently associated with tSUI on multivariate regression analysis.

This study is not devoid of limitations, including those inherent to a retrospective study. SUI characterization was primarily dependent on physician documentation. Missing data, especially from operative variables, also limited the robustness of the multivariable analysis. Comorbidities, such as diabetes, that may have been associated with SUI development were not adequately captured.

Regardless of these limitations, this study still represents the largest single-surgeon experience with HoLEP and provided valuable data regarding the incidence, time course and predictors of post-operative tSUI. Transient SUI after HoLEP has notable implications for patient quality of life, which may contribute to the hesitancy in the widespread adoption of HoLEP. Our study demonstrates this tSUI resolves in the majority of patients, usually within the first six weeks. Furthermore, by identifying risk factors that predispose patients to tSUI, preoperative counseling can be enhanced, thus mitigating possible patient frustration and improving both patient and physician satisfaction. This may also provide data for better patient selection in order to avoid these complications after the HoLEP procedure. We feel this study shows the need for future prospective trials and further inquiry into ways to prevent this complication.

CONCLUSIONS

Overall, our study helps to highlight the relatively low rate of incontinence (10.4%) seen after HoLEP from an experienced surgeon, with 8.8% being transient and 1.5% being long-term. Our results suggest that the overwhelming majority of patients with tSUI recover within the first 6 weeks following HOLEP. Prostate size greater than 100g and catheter dependency are associated with increased risk of developing tSUI, and larger prostate volume is an independent predictor of tSUI. While long-term SUI was rare (1.5%), it is possible that neurologic complications may be a contributing factor, though this requires further study. Those with long-term SUI are most often able to achieve continence with further intervention.

ABBREVIATIONS

SUI = Stress urinary incontinence
tSUI = Transient stress urinary incontinence
HoLEP = Holmium laser enucleation of prostate
BPH = Benign prostatic hyperplasia
LUTS = Lower urinary tract symptoms
TURP = Transurethral resection of prostate
PVR = Post-void residual
OP = Open prostatectomy
Qmax = Peak flow
IPSS = International prostate symptom score
QOL = Quality of life
PSA = Prostate-specific antigen
Fr = French

CONFLICT OF INTEREST

None declared.

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Supplementary Table 1.1 - Results from multivariable logistic regression analysis assessing for risk factors for any SUI in HoLEP patients.

Variables	OR (95% CI)	p
Age (years)	0.981 (0.928-1.037)	0.494
BMI (Kg/m^2)	0.983 (0.923-1.047)	0.597
Prostate Volume (mL)	1.009 (0.997-1.021)	0.133
Laser Energy Used (Kj)	0.990 (0.996-1.003)	0.763
Laser On Time (min)	0.997 (0.990-1.005)	0.463
Resected Prostate Volume (cc)	1.020 (1.007-1.033)	0.002

Supplementary Table 1.2 - Results from multivariable logistic regression analysis assessing for risk factors for tSUI in HoLEP patients.

Variables	OR (95% CI)	p
Age (years)	1.013 (0.949-1.083)	0.694
BMI (Kg/m^2)	0.987 (0.925-1.054)	0.697
Prostate Volume (mL)	1.011 (0.997-1.025)	0.113
Laser Energy Used (Kj)	1.001 (0.996-1.006)	0.731
Laser On Time (min)	0.995 (0.986-1.004)	0.259
Resected Prostate Volume (cc)	1.019 (1.006-1.032)	0.004

Supplementary Table 1.3 - Results from multivariable logistic regression analysis assessing for risk factors for long-term SUI in HoLEP patients.

Variables	OR (95% CI)	p
Age (years)	0.915 (0.825-1.014)	0.090
BMI (Kg/m^2)	0.964 (0.830-1.120)	0.630
Prostate Volume (mL)	1.002 (0.978-1.026)	0.896
Laser Energy Used (Kj)	0.997 (0.990-1.003)	0.345
Laser On Time (min)	1.006 (0.994-1.019)	0.308
Resected Prostate Volume (cc)	1.009 (0.985-1.034)	0.456

ORIGINAL ARTICLE

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The impact of perioperative complications on favorable outcomes after artificial urinary sphincter implantation for post-prostatectomy incontinence

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ABSTRACT

Objective: To investigate the effect of perioperative complications involving artificial urinary sphincter (AUS) implantation on rates of explantation and continence as well as health-related quality of life (HRQOL).

Materials and methods: Inclusion criteria encompassed non-neurogenic, moderate-to-severe stress urinary incontinence (SUI) post radical prostatectomy and primary implantation of an AUS performed by a high-volume surgeon (>100 previous implantations). Reporting complications followed the validated Clavien-Dindo scale and Martin criteria. HRQOL was assessed by the validated IQOL score, continence by the validated ICIQ-SF score. Statistical analysis included Chi (2) test, Mann-Whitney-U test, and multivariate regression models ($p < 0.05$).

Results: 105 patients from 5 centers met the inclusion criteria. After a median follow-up of 38 months, explantation rates were 27.6% with a continence rate of 48.4%. In the age-adjusted multivariate analysis, perioperative urinary tract infection was confirmed as an independent predictor of postoperative explantation rates [OR 24.28, 95% CI 2.81-209.77, p=0.004). Salvage implantation (OR 0.114, 95% CI 0.02-0.67, p=0.016) and non-prostatectomy related incontinence (OR 0.104, 95% CI 0.02-0.74, p=0.023) were independent predictors for worse continence outcomes. Low visual analogue scale scores (OR 9.999, 95% CI 1,42-70.25, p=0.021) and ICIQ-SF scores, respectively (OR 0.674, 95% CI 0.51-0.88, p=0.004) were independent predictors for increased HRQOL

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outcomes. Perioperative complications did not significantly impact on continence and HRQOL outcomes.
Conclusion: Findings show postoperative infections adversely affect device survival after AUS implantation. However, if explantation can be avoided, the comparative long-term functional results and HRQOL outcomes are similar between patients with or without perioperative complications.

INTRODUCTION

Current guidelines recommend surgical management of patients with persistent stress--urinary incontinence (SUI) (1-3). Reflective of the high success rates current treatment algorithms recommend the artificial urinary sphincter (AUS) as the gold standard treatment option for persistent moderate-to-severe SUI (1, 3, 4). Even though there are alternative devices available, the AMS 800® (Boston Scientific, USA) is the most frequently used AUS, and low-grade evidence suggests that outcomes may be superior compared to less frequently used devices (5). Our working group has recently demonstrated that intraoperative complications, postoperative bleeding and urinary tract infection as well as wound healing concerns are independent risk factors for short-term device explantation (6). However, the study did not evaluate the impact of perioperative complications on long-term functional outcomes. In addition, the inclusion of data from low-volume centers may limit generalized applicability of results (6).

Perioperative morbidity after AUS implantation is significant as demonstrated by a recent meta-analysis (7). Despite these findings, the impact of perioperative complications on long-term outcomes after AUS implantation is not fully understood. In this current study, we aim to evaluate the ramifications of perioperative complications on long-term functional and health-related quality of life (HRQOL) outcomes as well as the impact on device survival.

MATERIALS AND METHODS

Patient cohort, inclusion and exclusion criteria

The "Debates on Male Incontinence (DOMINO)" database is an international multi-institutional database that includes clinical data from 1047 male patients who have undergone implantation of a continence device due to SUI between 2010 and 2012 in one of 18 regional incontinence surgery referral centers. The inclusion criteria for the current study encompassed the following parameters: Non-neurogenic, moderate-to-severe SUI (≥3 pads) and primary implantation of a single-cuff AUS between 2010 and 2012 in a high--volume center (>100 previous implantations). In total, 105 patients from five different centers were eligible to participate in the current study. The surgical approach followed recommendations by national working groups on male urinary incontinence (8). The perioperative treatment course including perioperative antibiotic prophylaxis and time to trial without catheter (TWOC) varied slightly between the respective centers.

Study design, data assessment, definitions

Independent urologists, (not involved with the referral centers), performed the entire data assessment. After approval by a local ethics committee (University of Frankfurt, #442/13), questionnaires were sent per mail and information about the functional outcome was accrued. Medical records were interrogated/reviewed for perioperative complications (postoperative bleeding, wound healing disorders, acute urinary retention, infection, and de-novo urgency) and the perioperative course of action including time to TWOC, antibiotic prophylaxis and therapeutic management. The validated Clavien-Dindo scale was implemented to grade complications (9). Reporting of surgical complications followed the Martin criteria and is therefore consistent with current urologic guidelines (10, 11).

Notably, defined infections were not limited to devices only and included any clinical presentation for fever, local tenderness, erythema and/or abscess. De-novo urgency and acute urinary retention were only considered if requiring interventional management (e.g. catheterization). Scrotal hematoma represented postoperative bleeding. Outpatient data was appraised to gain detai-

led information about etiology and explantation rates respectively.

The following validated tools were employed to assess functional outcomes: International Consultation on Incontinence Questionnaire in its short form (ICIQ-SF) (12) and the International Quality of Life (IQOL) score (13). Continence was defined as the usage of up to a single daily safety pad (dry).

Statistical analysis

In this study, we assessed device survival, continence outcomes and quality of life. The Chi2 test was applied for categorical data analysis whereas Spearman's rank correlation and Kruskal-Wallis test evaluated continuous data. A Kaplan-Meier curve was implemented together with log-rank tests to analyze device survival. Multivariate analysis required application of binary logistic regression models. All statistical analyses were performed using SPSS V23.0 (IBM, USA). A p value <0.05 was considered to be statistically significant.

RESULTS

Patient characteristics, complications, perioperative treatment courses

Median follow-up was 38 (min 25 - max 58) months. Three out of four deaths during the follow-up period were from non-prostate related causes, a single patient passed away from progressive prostate cancer. There was no recorded procedure-related mortality. Functional outcome data was available for 75.0% of the remaining patients.

Mean duration of perioperative antibiotic treatment was 7.8±4.1 days. 37.5% of the patients received a single-shot antibiotic prophylaxis. Detailed patient characteristics as well as perioperative complications are summarized in Table-1.

Explantation rates

Within the follow-up period, 29 devices have been explanted, leading to an explantation rate of 26.7%. The causes for device explantation included urethral erosion (n=12), device infection (n=8), urethral atrophy (n=3), fistula (n=2), device dislocation (n=1), and continence failure (n=1).

Univariate analysis (Table-2) demonstrated postoperative UTI (88.9 vs. 22.6%, p <0.001) as well as any other postoperative complications (60.4 vs. 0.0%, p <0.001) significantly increased explantation rates. In patients with previous pelvic radiation there were no increased explantation rates (30.0 vs. 26.7%, p=0.810).

In age-adjusted multivariate analysis UTI was confirmed as an independent predictor of postoperative device explantation [odds ratio (OR) 24.28, 95% confidence interval (CI) 2.81 - 209.77, p=0.004).

Continence outcomes

We found a mean pad usage of 1.2±1.1 per day, representing a continence rate of 48.4%. 93.8% would recommend the AUS device to a friend and would undergo AUS implantation again. Mean ICIQ-SF score was 7.7±5.0.

The impact of perioperative complications on continence outcomes using univariate analysis is summarized in Table-2. In summary, we did not observe significantly altered continence rates despite perioperative complications. We found significantly decreased continence rates for patients with non-PPI (60.9 vs. 39.1%, p=0.017) as well as a statistical trend towards decreased continence rates in patients undergoing salvage AUS implantation (59.4 vs. 26.7%, p=0.059).

In multivariate analysis, adjusted for patient's age, independent predictors for worse continence outcomes were salvage implantation (OR 0.114, 95% CI 0.02 - 0.67, p=0.016) and non-PPI (OR 0.104, 95% CI 0.02 - 0.74, p=0.023).

HRQOL outcomes

Mean postoperative IQOL score was 84.8±22.5 (median 93). For further analysis of HRQOL outcomes, patients were divided into two groups depending on the respective IQOL score (<93 vs. ≥93). In univariate analysis (Table-2), postoperative HRQOL was significantly impacted by postoperative pain based on VAS ("yes" vs. "no"; 65.5 vs. 18.8%, p=0.004). Continent patients were found to have significantly better HRQOL (68.2 vs. 30.3%, p=0.017), ICIQ-SF scores (p <0.001) as well as lower postoperative daily pad usage (p=0.003).

In multivariate analysis adjusted for patient's age, a VAS pain score of 0 (OR 9.999,

Table 1 - Patient characteristics of 105 patients that met the inclusion criteria and were included in the current study.

No. of patients	105
Preoperative patient characteristics	
Age [yrs; mean±SD]	70.1±7.0
Post-prostatectomy SUI	83 (79.0)
BMI [kg/m2; mean±SD]	27.5±3.8
Pelvic external beam radiation [n (%)]	30 (28.6)
Duration of SUI [yrs; mean±SD]	5.2±4.8
Preoperative daily pad use [mean±SD]	7.0±2.8
Salvage implantation [n (%)]	32 (30.5)
Surgical procedure	
Perineal AUS [n (%)]	50 (47.6)
Penoscrotal AUS [n (%)]	55 (52.4)
Operation time [min; mean±SD]	76.3±30.9
Intraoperative complication [n (%)]	6 (5.7)
Catheter indwelling time [d; mean±SD]	2.9±1.0
Hospitalization period [d; mean±SD]	6.3±2.7
Perioperative complications	
Bleeding [n (%)]	5 (4.8)
Impaired wound healing [n (%)]	5 (4.8)
UTI [n (%)]	8 (7.6)
Urinary retention [n (%)]	10 (9.5)
Pain [VAS >0; n (%)]	9 (8.6)
De-novo urge [n (%)]	4 (3.8)
Perioperative complications [Clavien scale]	
Clavien I [n (%)]	18 (17.1)
Clavien II [n (%)]	7 (6.7)
Clavien IIIa [n (%)]	5 (4.8)
Clavien IIIb [n (%)]	35 (33.3)
Clavien IV [n (%)]	0 (0.0)
Clavien V [n (%)]	0 (0.0)

AUS = artificial urinary sphincter, **BMI** = body-mass index, **SD** = standard deviation, **SUI** = stress urinary incontinence, **UTI** = urinary tract infection, **VAS** = visual analogue scale

Table 2 - Univariate analysis of the effect of selected perioperative complications on postoperative explantation rates, continence rates, and health-related quality of life based on the validated I-QOL score after a median follow-up of 38 months. The I-QOL cut-off score of 93 is based on the median score of the entire cohort.

Complication	Explantation (%)	p value	Continence [%]	p value	IQOL≥93 [%]	p value
Radiotherapy [yes/no]	30.0 / 26.7	0.810	37.3 / 55.7	0.168	60.0 / 77.3	0.609
Intraoperative complication [yes/no]	10.3 / 3.9	0.343	33.3 / 50.0	0.516	66.7 / 47.6	0.608
Bleeding [yes/no]	60.0 / 26.0	0.128	50.0 / 46.8	0.889	0.0 / 50.0	1.000
Wound healing disorder [yes/no]	60.0 / 26.0	0.128	50.0 / 47.8	1.000	0.0 / 50.0	1.000
Urinary retention [yes/no]	50.0 / 25.3	0.135	50.0 / 47.8	1.000	0.0 / 50.0	1.000
Pain [VAS 0 vs. any other]	55.6 / 25.0	0.094	56.7 / 35.3	0.228	65.5 / 18.8	**0.004**
Urinary tract infection [yes/no]	88.9 / 22.6	**<0.001**	33.3 / 50.0	0.667	66.7 / 44.7	0.403
De-novo urge [yes/no]	25.0 / 26.6	1.00	0.0 / 57.8	0.444	0.0 / 45.5	1.000

VAS=visual analogue scale

95% CI 1.42 - 70.25, p=0.021) and lower ICIQ-SF scores (OR 0.674, 95% CI 0.51 - 0.88, p=0.004) were confirmed as independent predictors for improved HRQOL outcomes.

DISCUSSION

The current study investigates the impact of perioperative complications on long-term outcomes after AUS implantation. Our working group has described various complications following AMS 800 and adjustable male sling implantation for moderate-to-severe SUI (14). This study however further refined the inclusion criteria, limiting accrual to male patients with primary AUS implantation for moderate-to-severe non-neurogenic SUI in high-volume centers between 2010 and 2012. Moreover, this provides a homogenous patient cohort comparative to previous studies. Our comprehensive analysis of investigating continence outcomes after AUS implantation, device explantation rates and HRQOL allows our study to provide a more global view on favorable outcomes and overcome major shortcomings of previous studies (6, 15).

In the current study, we assess the impact perioperative complications have on long-term device explantation rates. Hereby, we confirmed previous evaluations regarding the effect of perioperative complications on 90-days explantation rates (6). In line with previous reports, we observed the most common cause to be postoperative infections. In addition, we found statistical trends towards higher explantation rates after postoperative bleeding, wound healing concerns or urinary retention. Our results are in line with findings of Linder et al., describing adverse short-term device survival after urinary retention. Furthermore cardiovascular disease, body-mass index, history of pelvic external beam radiation and previous invasive incontinence measures did not negatively impact short-term device survival (16). However, other studies describe a worse outcome or increased complication rates for irradiated patients (17, 18). In spite of the major impact perioperative infections has on our contemporary patient cohort, we did not find a significant benefit of the perioperative antibiotic treatment regime (duration of treatment, single-shot prophylaxis) on explantation rates. Despite increasing appreciation for risk factors affecting device infection and consecutive urethral erosion after AUS implantation, evidence regarding optimal perioperative antimicrobial management remains limited (19, 20). In a re-

cent review article, Hofer and Gonzalez concluded that strict perioperative antibiotic prophylaxis and sterile surgical technique seem to be crucial for acceptable surgical outcomes (21). However, the authors did not discuss the optimal duration of antimicrobial prophylaxis treatment. In addition, evidence suggests that antibiotic coating of the AUS does not decrease postoperative device infection rates (22). Due to the lack of evidence, antimicrobial prophylaxis regimens still vary significantly between institutions.

Naturally, a favorable outcome after AUS implantation implies adequate continence outcomes as well as adequate long-term HRQOL. In this contemporary patient cohort, we observe continence rates (defined as the need for up to one dry safety pad) of 48.4%. These results are in accordance with the 4% to 86% described in a meta-analysis by van der Aa et al. (7). In assessing predictive factors for functional outcomes, we found significantly worse continence rates for patients undergoing salvage surgery as well as for non-PPI patients. This is partly in contrast with existing literature. Interestingly, a retrospective single-center analysis of 64 patients demonstrated previous invasive incontinence treatments had no significant impact on continence rates following AUS implantation (20). However, considering previous invasive continence therapies may affect the regenerative potential of tissue within the surgical field, contributing to secondary tissue scarring, the subsequent AUS implantation may be more complex. In addition, patients suffering from non-radical prostatectomy related SUI (e.g.TUR-P or HIFU), may be prone to more severe extrinsic urinary sphincter damage, which in turn may manifest in worse continence results after AUS implantation. At present, possible mechanisms are not fully understood and warrant further investigation in larger patient cohorts.

To our knowledge, this is the first study investigating the impact of perioperative complications during AUS implantation on long-term continence and HRQOL outcomes. Our findings have several clinical implications. Firstly, we confirm the adverse effect of perioperative complications on device survival after AUS implantation. However, long-term continence and HRQOL outcomes seem to be comparatively similar between patients with or without perioperative complications if explantation can be avoided. Therefore, secondly, appropriate patient counseling is of imminent importance.

This study is not devoid of limitations. First and foremost are the limitations that are inherent to retrospective analyses in general. Even though the follow-up was assessed using standardized questionnaires, preoperative diagnostics were based on institutional pathways and not standardized. Furthermore, due to the multi-institutional design of this study, individual learning curves may impact on favorable outcomes (23). Lastly, the limited sample size of the current study, warrants future studies, with larger patient cohorts, to validate our results.

CONCLUSIONS

This study investigated data from high-volume continence referral centers, focusing on primary implantation of single-cuff artificial urinary sphincters by adequately experienced surgeons. We observed significantly increased explantation rates for patients with postoperative urinary tract infections. However, despite some perioperative complications the avoidance of explantation did not significantly affect functional outcome or postoperative HRQOL. Due to the small number of postoperative complications, larger studies with higher event rates are needed to confirm these findings.

ABBREVIATIONS

AUS = artificial urinary sphincter
HRQOL = health-related quality of life
ICIQ-SF = International Consultation on Incontinence Questionnaire short form
IQOL = International Quality of Life score
PPI = Post-prostatectomy incontinence
SUI = stress urinary incontinence
TWOC = time to trial without catheter
UTI = urinary tract infection

CONFLICT OF INTEREST

A. Kretschmer declares speaker fees for Boston Scientific (USA). R. M. Bauer declares

consultancy work, lectures, and participation in clinical trials for AMS (USA) and Promedon (Argentina). T. Pottek declares consultancy work, lectures for AMS, Zephyr (Switzerland), and Teleflex (USA). R. Anding declares consultancy work, lectures, and participation in clinical trials for AMS. C.M. Naumann declares consultancy work, lectures, and participation in clinical trials for Coloplast (Denmark). The remaining authors have nothing to disclose.

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EDITORIAL COMMENT

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Editorial Comment: The impact of perioperative complications on favorable outcomes after artificial u rinary s phincter i mplantation f or post-prostatectomy incontinence

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COMMENT

The Artificial Urinary Sphincter (AUS) is considered the gold standard treatment of non-neurogenic male urinary incontinence in several Guidelines (1-3). Despite the high rates of initial continence, a significant number of patients will need some type of revision, generally due to infection, urethral erosion, return of incontinence or mechanical problems (4). Failure rates and the need for revision are generally associated with patient characteristics and history of previous treatment - for the cancer or for urethral strictures. Several studies compared the long-term results of AUS implantation with age, radiation therapy, urethroplasty, AUS reimplantation, hypogonadism, use of corticosteroids, smoking and other potential risk factors (5-8). Clearly, the preoperative characterization of the patient and his clinical history are fundamental for the establishment of results and complications expectations, which must be properly discussed with the patient to achieve the best satisfaction rates.

On the other hand, it is also important to observe the impact of perioperative complications on the late results of the implants. Among these perioperative complications we can mention: surgical infection, urinary infection (UTI), bleeding with the hematoma formation, urinary retention and unrecognized intra-operative urethral lesions. The clinical practice and the current literature demonstrate that these complications are directly related to rates of early explantation (9), but there is a lack of information about the long-term impact. In this study, the authors analyze the impact of perioperative complications in a group of 105 men who underwent an AUS implantation, in high volume centers, with an average follow-up of 38 months, focusing on the rates of explanation, continence and quality of life (10). The authors observed that the perioperative UTI was an independent risk factor for device explantation. When analyzing long-term continence rates, there was no relationship with any type of perioperative complication. The patients' quality of life was affected only by postoperative pain and obviously by the final result of continence.

The prevention of perioperative complications is essential to decrease the rates of explantation, as previously demonstrated, including a study by this group (11). This prevention involves the proper preoperative patient evaluation of, identification of risk factors and an appropriate surgical technique. Despite the importance of the UTI, as an independent factor in the rate of late explantation, we still do not have a standardization in the use of antibiotic prophylaxis, as demonstrated in the methodology of this multicenter study, where about 37% of patients used prophylaxis with a single dose against about 63% using antibiotics also in the postoperative period.

Despite the methodological limitations, also identified by the authors, this study highlights the importance of UTI as an isolated risk factor for long-term sphincter explantation, demonstrating the need for robust, prospective, multicenter studies, with a sufficient number of patients, to cover the gap

of information regarding antibiotic prophylaxis in AUS implants - regimens, timing and use of antibiotic coating devices

waiting line is full and it is better that they say, "with this doctor, it didn't hurt at all".

CONFLICT OF INTEREST

None declared.

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Effect of smoking cessation on sexual functions in men aged 30 to 60 years

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ABSTRACT

Purpose: We aimed to evaluate the effects of smoking cessation on the sexual functions in men aged 30 to 60 years.

Materials and Methods: Male patients aged 30 to 60 years that presented to the smoking cessation polyclinic between July 2017 and December 2018 were prospectively included in the study. The amount of exposure to tobacco was evaluated in pack-year. The patients filled the International Index of Erectile Function (IIEF) form before the cessation and six months after cessation of smoking. Patients were subgrouped according to age, education level and packs/year of smoking and this groups were compared in terms of IIEF total and all of the IIEF domains.

Results: The evaluations performed by grouping the patients according to age (30-39, 40-49 and 50-60 years) and education level (primary-middle school and high school-university) revealed that the total IIEF scores obtained after smoking cessation were significantly higher compared to the baseline scores in all groups (p=0.007 for the 30-39 years group and p <0.001 for the remaining groups). According to grouping by exposure to smoking (≤25, 26-50, 51-75, 76-100 and 101≥ packs/year), the total IIEF scores significantly increased after smoking cessation in all groups except 101≥ packs/year (p=0.051 for the 101≥ group and p <0.001 for the remaining groups).

Conclusions: Erectile function is directly proportional to the degree of exposure to smoking, and quitting smoking improves male sexual function in all age groups between 30-60 years of age regardless of pack-year and education level.

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INTRODUCTION

Smoking, a widely present addiction around the World, can cause important health problems. It is reported that tobacco products contain around 4.000 chemical compounds, of which at least 60 are toxic (1). Many studies have shown the relationship between smoking and hypertension, acute coronary syndrome, angina, atherosclerosis, cerebrovascular diseases, and sudden death (2). Although the mechanism of this relationship has not yet been fully elucidated, it has been reported to lead to atherosclerosis as a result of vasomotor dysfunction, inflammation, and modification of lipids (3).

Erectile dysfunction (ED) is defined as the inability to achieve or maintain penile erection of adequate quality to achieve satisfactory sexual intercourse. ED is not a direct threat to life, but it

should also not be seen as a benign disorder because it is increasingly associated with cardiovascular diseases, such as ischemic cerebrovascular events, angina pectoris, myocardial acute insufficiency, and sudden death. Some authors have suggested that ED is a sentinel event and an early marker of cardiovascular diseases (4). According to the Massachusetts Male Aging Study (MMAS), 52% of men aged 40 to 70 years present varying degrees of erectile dysfunction (5). Endothelial dysfunction and microvascular damage play a role in the pathogenesis of ED. Among the main risk factors for this condition are high systolic blood pressure, diabetes, obesity, smoking, and dyslipidemia. It is known that the significant risk factors associated with ED are also frequently seen in smokers (6). Reducing smoking, engaging in regular exercise, adopting a healthy diet, losing excess weight, controlling diabetes, and making positive lifestyle changes have proven to reduce the risk of ED and metabolic syndrome (7).

There are several hypotheses on the physiopathological effects of long-term smoking on sexual dysfunction. Smooth muscle relaxation due to sexual arousal is a complex neurovascular event, in which arterial access to the genital area is provided and vasocongestion is facilitated (8). Nitric oxide (NO) produced in the genital endothelial cells has been defined as the main neurotransmitter mediating vascular events (9, 10). It has also been shown that smoking is associated with decreased NO in the veins (11). In light of these findings, researchers have suggested that free radicals and other compounds present in tobacco products may reduce the synthesis of NO either directly or indirectly by targeting precursors, which leads to a decrease in genital vaso-occlusion (12-14).

In this study, we aimed to evaluate the effects of smoking cessation on the sexual functions of men aged 30 to 60 years.

MATERIALS AND METHODS

Following the approval of the ethics committee, male patients aged 30 to 60 years that presented to the smoking cessation polyclinic between July 2017 and December 2018 were prospectively included in the study. The inclusion criteria were: having no psychiatric disease, not using alcohol or drugs, having no systemic disease, having no history of surgery, having a body mass index (BMI) of 20 to 25kg/m2, not using any tobacco product after cessation of smoking, not being a passive smoker, not having received any medical or surgical treatment for ED, and having a regular sexual partner. The amount of exposure to tobacco was evaluated in pack-year. Drugs for smoking cessation were given to the patients according to the avalibility of drugs in the hospital. The majority of patients (172/181, 95%) used Varenicline 1mg tablets 2x1/day and a small number of patients (9/181, 5%) received Bupropion HCL 150mg tablets 2x1/day for three months. The patients were asked to complete the International Index of Erectile Function (IIEF) form before and six months after cessation of smoking. In the erectile function (EF) domain of the IIEF questionnaire (items 1, 2, 3, 4, 5 and 15, range 0-5, max score 30), a score lower than 10 indicates severe ED, 11-16 moderate ED, 17-25 mild ED, and 26-30 normal EF. In the evaluation of IIEF-EF stage improvement, transitions from severe to moderate ED, from moderate to mild ED, or from mild ED to normal EF groups were accepted as improvement (+) in EF. The remaining domains of IIEF are intercourse satisfaction containing items 6 to 8 (range 0-5, max score 15), orgasmic function with items 9 and 10 (range 0-5, max score 10), sexual desire with items 11 and 12 (range 0-5, max score 10), and overall satisfaction with items 13 and 14 (range 0-5, max score 10). Patients were subgrouped according to age, education level and packs/year of smoking and these groups were compared in terms of IIEF total and all of the IIEF domains.

The analyses of data were performed with the Statistical Package for the Social Sciences software for Windows (SPSS, Inc., Chicago IL) version 22, and the data were presented as mean±standard deviation and numbers (n) and percentages (%). Student's paired t-test was used for the comparison of the domain scores of the IIEF questionnaire before and after smoking cessation and one-way ANOVA test to evaluate the association between smoking exposure and ED severity. P values of <0.05 were considered as statistically significant.

RESULTS

A total of 202 patients were evaluated, 21 of them restarted to smoke and were excluded from the study, and finally 181 patients were included in the study. The mean age of patients was 47.7±9.6 (min 30-max 60) years, and the mean pack-year was 46.1±32.2 (min 5-max 160). The total IIEF score was 54.8±16.7 (min 9-max 75) before smoking cessation and 60.4±15.3 (min 15-max 75) after smoking cessation.

The evaluations performed by grouping the patients according to age (30-39, 40-49 and 50-60 years) and education level (primary-middle school and high school-university) revealed that the total IIEF scores obtained after smoking cessation were significantly higher compared to the baseline scores in all groups (p=0.007 for the 30-39 years group and p <0.001 for the remaining groups) (Table-1). According to grouping by exposure to smoking (≤25, 26-50, 51-75, 76-100 and 101≥ packs/year), total IIEF scores were significantly increased after smoking cessation in all groups except 101≥ packs/year (p=0.051 for the 101≥ group and p <0.001 for the remaining groups) (Table-1). Stage improvement was observed in 25.4% of the patients, but no statistically significant difference was found between the age groups, pack-year groups, or education level groups (p=0.124, p=0.052 and p=0.475, respectively) (Table-1).

In a separate comparison undertaken according to the IIEF domain scores, it was found that all domain scores significantly increased after smoking cessation (Table-2).

The IIEF-EF scores also significantly increased in the severe, moderate and mild ED groups,

Table 1 - Comparison of the total IIEF scores and stage improvement status before and after smoking cessation in age, pack-year and education level groups.

	Smoking (+)	Smoking (-)	P	Stage	Stage	p
	Total IIEF score (mean ± SD)	Total IIEF score (mean ± SD)		improvement (-) 135 (74.6%)	improvement (+) 46 (25.4%)	
Age groups (years)						0.124
1) 30-39 (n=38)	27.4 ± 4.4	28.9 ± 2.6	0.007	33 (86.8%)	5 (13.2%)	
2) 40-49 (n=47)	23.8 ± 4.1	26.2 ± 3.5	<0.001	35 (74.5%)	12 (25.5%)	
3) 50-60 (n=96)	18.3 ± 7.7	21.4 ± 7.4	<0.001	67 (69.8%)	29 (30.2%)	
Pack-year groups						0.052
1) 25≤ (n=63)	23.3 ± 7.9	25.6 ± 6.8	<0.001	44 (69.8%)	19 (30.2%)	
2) 26-50 (n=56)	22.7 ± 5.2	26.1 ± 4.1	<0.001	44 (78.6%)	12 (21.4%)	
3) 51-75 (n=27)	19.0 ± 8.4	20.9 ± 6.8	<0.001	22 (81.5%)	5 (18.5%)	
4) 76-100 (n=25)	18.3 ± 7.6	20.8 ± 8.0	<0.001	21 (84.0%)	4 (16.0%)	
5) 101≥ (n=10)	20.2 ± 6.5	22.6 ± 6.3	0.051	4 (40.0%)	6 (60.0%)	
Education level groups						0.475
1) Primary - middle school (n=79)	22.5 ± 7.5	24.9 ± 7.0	<0.001	61 (71.2%)	18 (28.8%)	
2) High school - university (n=102)	21.0 ± 7.2	23.7 ± 6.2	<0.001	74 (72.5%)	28 (27.5%)	

IIEF = International Index of Erectile Function

Table 2 - Comparison of the IIEF domain scores before and after smoking cessation.

IIEF domains (item number)	Smoking (+)	Smoking (-)	P
	IIEF domain score (mean±SD)	IIEF domain score (mean±SD)	
EF (1,2,3,4,5,15)	21.6 ± 7.3	24.2 ± 6.6	<0.001
Intercourse satisfaction (6,7,8)	10.5 ± 3.5	11.7 ± 3.2	<0.001
Orgasmic function (9,10)	8.6 ± 2.4	8.9 ± 2.1	<0.001
Sexual desire (11,12)	6.8 ± 2.0	7.7 ± 1.9	<0.001
Overall satisfaction (13,14)	7.2 ± 2.5	8.0 ± 2.0	<0.001

IIEF = International Index of Erectile Function, **EF** = Erectile Function

but not in the normal-EF group after smoking cessation (Table-3).

When severe ED, moderate ED, mild ED and normal EF groups determined according to the IIEF-EF domain score were compared in terms of the mean pack-year, it was seen that EF deteriorated with increasing exposure to smoking (p <0.001) (Table-4).

DISCUSSION

Penile erection is largely caused by the presence of sufficient blood flow into the erectile tissue, simultaneous arterial endothelium-dependent dilatation, and sinusoidal endothelium-dependent corporal smooth muscle relaxation (15). Free radicals, aromatic compounds and superoxide anions in the smoke of tobacco products can disrupt dilation by impairing NO synthesis and degradation in the penile artery and arterioles (16). In addition, smoking is an independent risk factor for atherosclerosis in internal, pudental and common penile arteries (17). Considering these mechanisms, the development of ED is an expected outcome in smokers. Furthermore, it is suggested that the risk of ED increases with the elevated amount of exposure to cigarette toxins, smoking accompanied by aging, and cavernosal arterial occlusive conditions, such as hypertension and diabetes mellitus (5, 17).

Nicotine replacement therapy and non--nicotine drugs are the most commonly used pharmacological treatments in tackling smoking addictions. Bupropion is a well-tolerated medication used in smoking cessation to reduce withdrawal symptoms during treatment and weight gain after quitting smoking (18, 19). Varenicline also has nicotinic agonist effects that stimulate α4 β2 receptors and provide dopamine release from the

Table 3 - Comparison of the IIEF-EF domain scores of the IIEF-EF categories before and after smoking cessation.

IIEF-EF categories (baseline evaluation)	Smoking (+)	Smoking (-)	p
	IIEF-EF domain score (mean±SD)	IIEF-EF domain score (mean±SD)	
1) Severe ED (score ≤10) (n=14)	5.2 ± 2.4	8.2 ± 3.9	0.009
2) Moderate ED (score 11-16) (n=19)	12.5 ± 1.0	16.7 ± 3.8	<0.001
3) Mild ED (score 17-25) (n=93)	21.3 ± 2.8	24.9 ± 3.2	<0.001
4) Normal EF (score 26-30) (n=55)	29.5 ± 1.2	29.7 ± 0.8	0.061

IIEF-EF = International Index of Erectile Function-Erectile Function, **ED** = Erectile dysfunction

Table 4 - Comparison of the IIEF categories according to exposure to smoking.

IIEF-EF categories (baseline evaluation)	Exposure to smoking (packs/year) (mean±SD)	P
1) Severe ED (score ≤10) (n=14)	57.1 ± 39.6	< 0.001
2) Moderate ED (score 11-16) (n=19)	53.3 ± 23.8	
3) Mild ED (score 17-25) (n=93)	51.5 ± 35.4	
4) Normal EF (score 26-30) (n=55)	31.6 ± 20.6	

IIEF-EF = International Index of Erectile Function-Erectile Function, **ED** = Erectile dysfunction

nucleus accumbens, which is followed by the antagonistic effect, meaning that there is no increase in dopamine release even if the person inhales nicotine when using varenicline. Through these agonist and antagonist functions, varenicline decreases nicotine dependence and prevents the occurrence of withdrawal symptoms (20).

Mannino et al. reported that the incidence of ED increased in smokers and decreased after smoking cessation in their study conducted with 4.500 Vietnam War veterans (21). Guay et al. found that in patients who previously smoked more than 30 packs/year, there was rapid improvement in penile integrity and rigidity one month after smoking cessation. The authors noted that according to the study data, this improvement was more significant in the younger age group and in the absence of additional diseases that might pose risk for ED (22). In contrast, in our study, we found that improvement was more significant in the older age group. This may be due to the absence of additional systemic diseases and the maximum age of our sample being 60 years.

Pourmand et al. investigated the effects of smoking cessation and continuation of the non--smoker status in patients with ED. They found that the severity of ED was significantly related to the level of exposure to smoking. After one year of follow-up, the authors detected improvement in EF in ≥25% of ex-smokers but in none of the persistent smokers. Furthermore, 2.5% of the ex-smokers and 6.8% of persistent smokers had deterioration in the ED status. Better EF was observed in the follow-up of ex-smokers. It was also reported that among those who stopped smoking, older cases had the least improvement in EF (23). In the current study, we only included patients that stopped smoking and did not start it again. Fifty-five of the patients that were followed up (30.4%) consisted of ex-smokers with normal EF. We found a direct correlation between exposure to smoking (pack/year) and the negative effect of smoking on EF. In terms of smoking categories according to package/years, the total IIEF scores positively increased in all groups after smoking cessation. Furthermore, this increase was not statistically significant only in the ≥101 packs/year group (excessive exposure to smoking). In our study, we found no positive effect of stopping smoking on the EF of patients with a normal IIEF-EF score (26 to 30) before smoking cessation. However, in all categories of IIEF-EF, we detected positive improvement after smoking cessation. In addition, we detected 25.4% stage improvement similar to the result reported by Pourmand et al. In contrast, in the current study, we did not observe any ED at the end of six months. Moreover, contrary to Pourmand et al., the greatest stage improvement (30.2%) occurred in the elderly group of our study (50-60 years). We also found that stage improvement was not significantly correlated with age, exposure to smoking, and education level. As an additional finding of our study, we found improvement not only in the IIEF-EF domain but also in the evaluation of intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction after smoking cessation. This may be due to not only improved EF, but also changes in serum testosterone levels with the discontinuation of smoking, although there are conflicting reports in the literature (24-27).

The main limitation of this study was that early (e.g., first-month) and late outcomes after smoking cessation were not evaluated. The second limitation of study was the restrictive age group of patients; the results can not be generalized to older patients. However, the advantage of the study was the presence of a patient group independent of other factors that may affect EF.

CONCLUSIONS

In conclusion, EF is directly proportional to the degree of exposure to smoking, and stopping smoking improves male sexual function in all age groups between 30-60 years of age regardless of number of packs-year and education level.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Effect of smoking cessation on sexual function in men aged 30 to 60 years

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COMMENT

This study involved 181 relatively young individuals (30-60 years) who were former smokers and had no other risk factor for erectile dysfunction (ED) besides smoking. The participants completed the IIEF during the first consultation, while still under the effects of smoking, and again six months later. As expected, the prevalence of ED was significantly lower after smoking cessation (1).

While much is focused on smoking and its association with cancer and cardiovascular disease, which occur in older individuals, few studies address the effects on young people and adolescents, who can suffer the same adverse effects, including ED. There are approximately one billion smokers in the world and every year eight million people die due to smoking and its adverse effects (2).

The pathophysiological mechanism of endothelial dysfunction results from an inhibition of the nitric oxide cascade, preventing adequate arterial dilation and the blood flow necessary for penile erection. In addition to endothelial dysfunction, smoking is also a risk factor for arteriosclerosis (3-5). Sahin MO et al., the authors of the study commented here, also mention the correlation between ED and cardiovascular disease and smoking as a risk factor for both (1).

In smokers with heart disease, the risk of complete ED is seven times higher than that imposed by any of the risk factors alone (6). In an analysis of more than 31,000 individuals over 50 years of age, the prevalence ED was 33% and was higher among those who were obese, sedentary, smokers and alcoholics (7). These data were confirmed in several other studies (8, 9).

This study offers insight into contemporary indications that smoking is significantly associated with ED and smoking cessation has a beneficial effect on the restoration of erectile function (EF). The literature offers studies showing the association between smoking and hypertension, acute coronary syndrome, angina, atherosclerosis, cerebrovascular diseases and sudden death. Based on this consistency, a fair conclusion may be drawn that male sexual function and smoking have a temporal relation; smoking precedes ED. There is an increased risk of ED with greater exposure to smoking and smoking cessation can lead to the recovery of erectile function but only if lifetime exposure to smoking is limited (10, 11).

Based on this study, urologists should counsel smokers with ED to quit smoking, which will result in an improvement in erectile rigidity and tumescence.

CONFLICT OF INTEREST

None declared.

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Synthetic slings in the treatment of urinary incontinence: lessons learned and future perspectives

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COMMENT

In the past decades, the refinement of therapeutic solutions for stress urinary incontinence and pelvic organ prolapse have evolved almost in parallel. Although initial proposals for the use of synthetic suburethral slings date back to the 1990s (1), their use became widespread in the 1990s, notably through the development of monofilament polypropylene slings. After the publication of the Integral Theory (2) and its materialized surgical application, the Tension-Free Vaginal Tape (TVT) quickly became the new gold-standard treatment of stress urinary incontinence in women. Thereafter, retropubic mid-urethral slings evolved, through the novel use of the transobturator approach (3) in order to achieve similar effectiveness with lower rates of surgical complications. Lastly, minislings (4) stemmed from the effort to make the procedure even less invasive, however its possible indications and long-term effectiveness still demand further investigation (5,6). Regardless of the approach taken by each technique, it is clear that the large amount of high-quality trials on mid-urethral slings have set them among some of the most well studied procedures in contemporary Urology.

After the development of the first mid--urethral mesh slings, a will to use mesh for the repair of pelvic organ prolapses did not take long to follow. From the start of the 2000s onwards, there was a significant increase in de number of procedures using polypropylene prostheses, which obtained prompt approval from international regulatory agencies based on the principle of material equivalence with mid-urethral synthetic slings.

Stress urinary incontinence and pelvic organ prolapse do indeed share similar risk factors and are akin to each other in their pathophysiology, based on progressive degeneration of collagen fibers in pelvic floor tissues, notably their supporting conjunctive fascia. Both conditions tend to become more prevalent with continuing increases in life expectancy, therefore representing a potential public health challenge in the near future, even in countries with good standards of perinatal care. Be that as it may, when compared to those with stress incontinence, patients with pelvic organ prolapse present more complex anatomical changes and a myriad of clinical presentations, in which voiding, proctologic or sexual dysfunction symptoms may predominate, depending on the mostly affected vaginal compartment (anterior, apical or posterior).

Due to such diversity in clinical presentation, initial attempts to standardize and promote the treatment of pelvic organ prolapse using transvaginal meshes proved to be inadequate, unlike their mid-urethral sling counterparts years ago. As most mesh kits were unable to repair combined vaginal wall defects, large or combined prostheses were required, leading to the need to implant large amounts of synthetic material in the vagina. As the vaginal elasticity is the main determinant of its normal physiology, the implant of inextensible material to treat a prolapse could lead to a significant risk of complications, such as voiding dysfunction, chronic pain and sexual dysfunction resulted from the local fibroblastic reaction, which can assume a permanent and progressive pattern. Thus, the increased implantation of transvaginal prosthesis for the treatment of pelvic organ prolapse was followed by a marked rise in the frequency of such complications, alongside vaginal exposure or extrusion of prosthetic segments and erosion of surrounding pelvic viscera.

The initial reaction to this evidence came from the Food and Drug Administration (FDA) through the publication of alerts in 2009 and 2011 suggesting caution in the use of transvaginal meshes (7), and another in 2012, which ordered mandatory prospective studies conducted by the companies who shared that market (2012) (8). Such warnings triggered the reaction of the lay community, initially in the United States, directed indistinctly against transvaginal meshes for POP as well as against synthetic mid-urethral slings, which included sensationalist reports published in the media, government inquiries and a significant increase in lawsuits against doctors and mesh manufacturer companies. The decision of Johnson & Johnson, one of the most relevant companies in the field, to withdraw from female pelvic medicine market in 2012, had great repercussions in North America and included not only prostheses for POP treatment, but also their mid-urethral sling brands.

On the other hand, international medical societies, such as the International Continence Society, International Urogynecological Association and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction, released statements in order to uphold the great advance that synthetic medium urethral slings posed in treatment of stress urinary incontinence, and also to determine scientific criteria for the use of transvaginal mesh in the treatment of pelvic organ prolapse, recommending its use specifically for recurrences and stage 3 and 4 prolapses, especially vaginal vault prolapses (9). In fact, since 2008, the FDA has also systematically differentiated the transvaginal mesh for POP from synthetic mid-urethral slings and excluded special warnings against synthetic slings from its recommendations in 2011. However, in 2016 the FDA reclassified transvaginal prostheses for POP from category 2 to category 3, in a category akin to other implants such as heart valves, pacemakers, cochlear implants and intraocular lenses. Mesh manufacturers also made an effort towards reducing the amount of synthetic material implanted in pelvic organ prolapse surgeries, through low weight meshes and the refinement of anchoring systems, which changed from transobturator and transgluteal fixation, used in the early transvaginal prostheses, to sacrospinal ligament fixation devices, intending to prevent the risk of muscle bleeding, nerve compression, severe chronic pain and sexual dysfunction. Despite the technical improvements, campaigns against transvaginal meshes became popular in the United Kingdom, Australia and New Zealand, which culminated in an almost complete abolishment of the use of transvaginal meshes and synthetic slings in those countries, increasing the animosity to polypropylene prostheses through the world.

Reluctance in the use of transvaginal mesh for pelvic organ prolapse has led to its replacement by sacral colpopexy/hysteropexy, mostly driven by developed countries due to an increased availability of robot-assisted laparoscopy, which shortened the conventional laparoscopy learning curve. Thus, sacral colpopexy/hysteropexy quickly came to be the new standard technique for the treatment of pelvic organ prolapses, particularly vaginal vault prolapses, despite scientific references still indicating the need for further studies (10-12). In comparison, the experience with the former transvaginal meshes for POP necessarily leads to reflections about the future consequences of lapa-

roscopically or robotically implanted meshes on vaginal elasticity and on the function of the pelvic floor, as some groups advised its fixation on the fascia of the levator ani muscle.

The aversion to synthetic slings rekindled the interest in fascial sling (13-15), which had been reserved mostly for complex cases or when incontinence was associated with specific conditions, such as urethral diverticula. Unlike in the 1990s literature, when evidence on aponeurotic slings was almost entirely based on case series with short or intermediate follow-up and a few unicentric prospective studies using homemade slings, nowadays the aponeurotic slings are being faced against commercially synthetic mid-urethral slings, using internationally validated and standardized objective and subjective healing criteria, applied in prospective multicenter randomized studies sometimes grouped by means of systematic review and meta-analysis techniques (16).

This ongoing trend has already provided the literature with evidence that tends to consider that the objective and subjective cure rates of synthetic and aponeurotic slings are similar, although aponeurotic slings have higher costs and more frequent adverse effects, even considering that modern aponeurotic slings became less wide and implanted in the urethra (17) instead in the bladder neck as originally proposed (18). From a qualitative point of view, recent research pointed out that nowadays aponeurotic slings are mainly performed by urologists, who are used to treating older patients with more comorbidities (19), and the risk of adverse events is directly related to surgical volume, being significantly lower for those surgeons who operated more than 50 cases per year (20).

In Brazil, synthetic medium urethral slings and some transvaginal meshes are still approved by the National Health Surveillance Agency and have been used by urologists and gynecologists based on their own judgment. Moreover, the fact that these treatments are barely offered by the Public Health System, and the higher age of the majority of patients with pelvic organ prolapse who seek medical assistance – most without great sexual expectations – could contribute to alleviate part of the eventual dissatisfaction generated by possible adverse effects. Nevertheless, it is highly recommended that a signed informed consent form is obtained, and the surgeon should maintain a prolonged post-operative follow-up in order to detect and treat adverse events as early as possible.

We must recognize that expectations regarding the treatment of stress urinary incontinence tend to irreversibly increase over the next years, since they are significantly enclosed in female quality of life. Moreover, a growing number of elderly women tend to practice physical activities regularly and remain sexually active for longer periods. Also, despite all efforts, research on how to modulate pelvic floor collagen degradation and remodeling through genetic engineering has not yielded any significant results yet, leaving surgical treatments as still the main therapeutic alternative for incontinence in the near future.

In conclusion, the proper use the synthetic mid-urethral slings and meshes for pelvic organ prolapse is now a choice of the pelvic floor reconstructive surgeon, should prioritize their use in ligament reinforcement rather than fascial replacement, while also committing to monitoring patients more carefully for longer. Simplistic solutions, such as the indistinct ban of promising technologies, or even a massive reinvigoration of old techniques previously replaced due to their adverse effects or their dissonance to modern pathophysiological concepts about incontinence, certainly do not represent the best alternative for the care of our patients.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ROBOTIC

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Editorial Comment: Laparoscopy versus robotic-assisted pyeloplasty in children: preliminary results of a pilot prospective randomized controlled trial

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COMMENT

This interesting paper reported a prospective randomized controlled trial (RCT) about laparoscopic and robotic pyeloplasty in the treatment of ureteropelvic junction obstruction (UPJO) in children. They addressed if the robotic-assisted laparoscopic pyeloplasty (RALP) has additional advantages over conventional laparoscopic pyeloplasty (LP) regarding suturing, comfort for the surgeon and visualization. The main disadvantage of RALP is its higher cost (1, 2). This is the first RCT comparing LP and RALP in pediatric population. In a period of 2 years, a total of 53 children (0–18 years old) with UPJO were enrolled into the RCT for either LP or RALP (Group 1, n: 27 - Group 2, n:26). The presence of crossing vessel was identified in 7 (25.9%) patients for LP group and in 6 (23.1%) patients for RALP group. Mean total operative time in LP group was 139.26 ± 43.21 min (80–250 min) compared to 105.19 ± 22.87 min (70–150 min) in RALP group (p = 0.001). The number of the trocar placement was significantly less in LP group (mean 3.00 ± 0) compared to RALP group (mean 3.81 ± 0.40) (p = 0.001). The mean cost of RALP was higher than LP (p = 0.001). They completed successfully all cases with none converted to open surgery. Postoperative complication rates were similar for both groups in the follow-up period. They reported overall success rate of 96.2%, similar to previously published series of minimally invasive pyeloplasty. Accordingly, robotic procedures had approximately four times higher cost than conventional laparoscopy (3). Despite small number of patients there was a as a pilot study, they reported a RCT and their findings are important to demonstrate the comparison of LP and RALP in children. The short-term results reveals that both LP and RALP are safe and effective in children with comparable success and complication rates.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ROBOTIC

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Editorial Comment: Does the Use of a Robot Decrease the Complication Rate Adherent to Radical Cystectomy? A Systematic Review and Meta-Analysis of Studies Comparing Open with Robotic Counterparts

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COMMENT

In this paper the group of university of Athens, performed a very good review and meta-analysis (using PRISMA guidelines) about complication rates of robotic assisted radical cystectomy (RARC). Despite open radical cystectomy (ORC) remains the mainstay of treatment for muscle-invasive and high-risk nonmuscle-invasive bladder cancer decreasing complication rates was the main goal of development of minimally invasive alternative techniques. RARC has been transforming into a safe and efficient alternative to the open gold standard procedure (1-3). This meta-analysis is the largest in the literature comparing complication rates between open and RARC. The advantages in terms of peri- and postoperative outcomes of this minimally invasive procedure has remained contradictory. A higher level of evidence is usually extracted by well-designed, randomized control studies and seems to agree with their findings that do not award the robotic procedure any advantage in terms of complication rates when compared with its open counterpart (3-6). They analyzed 54 studies (5 randomized trials and 49 observational), including 29,697 patients (6,500 in the RARC group and 23,197 in the open radical cystectomy group). RARC was associated with lower blood transfusion rates ($p < 0.001$), lower length of stay ($p < 0.001$), faster return to regular diet ($p < 0.001$),

and lower postoperative mortality rates ($p < 0.001$), but longer operating time. They concluded RARC appears to be associated with fewer complications and favoring perioperative outcomes in comparison with the ORC. RARC is an efficient and safe procedure that can provide an alternative to the open procedure.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ROBOTIC

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Editorial Comment: Robotic surgery using Senhance® robotic platform: single center experience with first 100 cases

Samalavicius NE[1,2], Janusonis V[3,4], Siaulys R[3], Jasenas M[3], Deduchovas O[3], Venckus R[3], Ezerskiene V[3], Paskeviciute R[3], Klimaviciute G[3]

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COMMENT

In this paper Dr Samalavicius, reported that robotic surgery today has already had a long tradition and use only option for performing robotic surgery (da Vinci robotic system), which has been the for almost past two decades. This paper describe a cohort using the Senhance® robotic system (TransEnterix Surgical Inc., Morrisville, NC, USA). In contrast to a previous existing robotic platform. This novel system has haptic feedback and the camera can be operated with an "eye-sensing control". After a successful cohort in gynecology and colorectal surgery. This system is approved in Europe and USA and pronounce lower costs per operation. This system uses standard surgical trocars and can be positioned in the typical laparoscopic positions for the different interventions. All surgeries included in their article were performed from November 2018 to March 2019 a total of 100 procedures using the Senhance® robotic platform in general and colorectal surgery, gynecology, and urology (31 procedures, of them 27 radical prostatectomies). There were 3 (3%) conversions: two to laparoscopy (both undergoing robotic radical prostatectomy) and one to open (undergoing total hysterectomy). The reasons for conversions to laparoscopy were technical difficulties for continuing with robotic surgery due to difficult pelvic anatomy, and unexpected findings for conversion to open surgery. Complication rate was reasonable and occurred in 16 patients (35.5%), but only 2 (4.4%) complications were severe (Clavien–Dindo III); none of his patients demanded reoperation. The authors reported their experience in radical prostatectomies using this system is the first in literature. They clarified that more detailed analysis about radical robotic prostatectomies will be published separated in near future

paper. They concluded the experience with different types of robotic surgeries allows them to state that the Senhance® robotic system is feasible and safe for general surgery, gynecology, and urology. They believe a wider implementation of this system worldwide is simply a question of time.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

PENILE CANCER
TESTICULAR CANCER

Editorial Comment: Practice Patterns and Impact of Postchemotherapy Retroperitoneal Lymph Node Dissection on Testicular Cancer Outcomes

Woldu SL #[1], Moore JA #[2], Ci B [3], Freifeld Y [1], Clinton TN [1], Aydin AM [4], et al.

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COMMENT

In this paper, Dr. Solomon L. Woldu, and colleagues, from University of Texas Southwestern Medical Center, Dallas, TX, USA, evaluated patterns of postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) use in the USA and evaluate the association between PC-RPLND and survival in advanced nonseminomatous germ cell tumors (NSGCTs).

They conduct a retrospective, observational study using National Cancer Data Base (NCDB) data from 2004–2014 for 5062 men diagnosed with stage II/III NSGCT.

PC-RPLND plays a central role in the multidisciplinary approach of patients with advanced testicular cancer, removing lymph nodes that may contain viable tumor or teratoma, with prognostic implications and impact on survival and

30% of patients after chemotherapy with visible persistent masses on examination and negative serum tumor markers are eligible for PC-RPLND because these masses can harbor viable GCT or teratoma.

The authors find that patients undergoing PC-RPLND were more likely to be younger, white, privately insured, and reside in more educated/wealthier regions ($p < 0.001$). Insurance status was independently associated with receipt of PC-RPLND; compared to patients with private insurance, those without insurance were significantly less likely to receive PC-RPLND.

After multivariate adjustment, age, comorbidity, non-private insurance, distance from hospital, clinical stage, and risk group were independently associated with all-cause mortality and omission of PC--RPLND remained associated with all-cause mortality (hazard ratio 1.98; $p < 0.001$).

These data reinforce the need to subject these patients to, because omission of PC-RPLND is associated with lower OS.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

PENILE CANCER
TESTICULAR CANCER

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Editorial Comment: Prevalence of human papillomavirus DNA and p16INK4a in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis

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COMMENT

In this paper, Tina Bech Olesens and colleagues, have assessed pooled HPV DNA prevalence in penile intraepithelial neoplasia or p16INK4a percent positivity in penile cancer and penile intraepithelial neoplasia and the prevalence of HPV DNA and p16INK4a positivity in penile cancer and penile intraepithelial neoplasia worldwide.

They made a systematic review and meta-analysis, in PubMed, Embase, and the Cochrane Library until July 24, 2017, for English-language articles published from Jan 1, 1986, onwards reporting the prevalence of HPV DNA and p16INK4a positivity, either alone or in combination, in at least five cases of penile cancer or penile intraepithelial neoplasia.

Using random-effects models, they estimated the pooled prevalence and 95% CI of HPV DNA and p16INK4a positivity in penile cancer and penile intraepithelial neoplasia, stratifying by histological subtype and HPV DNA or p16INK4a detection method. Type-specific prevalence of HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, and HPV45 in penile cancer was estimated.

The authors searches identified 1836 non-duplicate records, of which 73 relevant papers (71 studies) were found to be eligible. The pooled HPV DNA prevalence in penile cancer (52 studies; n=4199) was 50·8%. A high pooled HPV DNA prevalence was seen in basaloid squamous cell carcinomas and in warty-basaloid carcinoma. The predominant oncogenic HPV type in penile cancer was HPV16 followed by HPV6 and HPV18. The pooled HPV DNA prevalence in penile intraepithelial neoplasia (19 studies; n=445)

was 79·8%. The pooled p16INK4a percent positivity in penile cancer (24 studies; n=2295) was 41·6% (p <0·0001), with a high pooled p16INK4a percent positivity in HPV-related squamous cell carcinoma as compared with non-HPV-related squamous cell carcinoma. Moreover, among HPV-positive cases of penile cancer, the p16INK4a percent positivity was 79·6%, compared with 18·5% in HPV-negative penile cancers. The pooled p16INK4a percent positivity in penile intraepithelial neoplasia (six studies; n=167) was 49·5%.

In this interesting manuscript the authors concluded that a large proportion of penile cancers and penile intraepithelial neoplasias are associated with infection with HPV DNA (predominantly HPV16), emphasising the possible benefits of HPV vaccination in men and boys.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

MALE HEALTH

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Editorial Comment: Novel Treatment for Premature Ejaculation in the Light of Currently Used Therapies: A Review

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COMMENT

In this recent review, Dr. Hartmut Porst and Andrea Burri pointed the actual situation of Premature Ejaculation (PE) arguing that there is a gap between what doctors are prescribing and what patients expect from treatment.

The only so far officially approved medication – dapoxetine - is characterized by high discontinuation rates of up to 90%, mostly because of high side effects, cost issues, efficacy below expectations, and the need for scheduling sexual intercourse.

The authors discussed advantages and disadvantages of currently available off-label and officially approved treatment options and presented the dose-metered lidocaine-prilocaine spray (Fortacin™), the first topical treatment to be officially approved in Europe for the treatment of primary PE in adult men.

The use of drugs that selectively reduce penile sensitization or which modify the afferent-efferent reflex could provide effective therapy for PE, as has been shown with the off-label use of topical desensitizing creams (1) that represents the oldest form of pharmacotherapy in PE (1943).

There are many studies (2, 3) demonstrating safety and efficacy of this lidocaine-prilocaine spray (first known as TEMPE and also PSD502) that seems to have some advantages from creams, since its special galenic properties generates a stable mixture which can be readily absorbed through the glans penis mucous membrane, but not through normal keratinized skin, maximizing the extent of neural blockage and minimizing the onset of numbness (4).

Fortacin ™ was officially approved for use in the European Union in 2013 and finally launched in the United Kingdom in November 2016. This lidocaine-prilocaine spray, with all pharmacological advantages and well conducted trials, has not yet reached a significant first-line therapy status both for the physicians and the patients in PE. There are no comments from the authors to contradict or explain this fact.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

MALE HEALTH

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Editorial Comment: Erectile Dysfunction and Premature Ejaculation in Homosexual and Heterosexual Men: A Systematic Review and Meta-Analysis of Comparative Studies

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COMMENT

Dr. Arcangelo Barbonetti et al. published the first meta-analysis exploring the differences in the prevalence of ED and PE between homosexual and heterosexual men.

They found that homosexual orientation is associated with higher odds of erectile dysfunction (ED) and lower odds of premature ejaculation (PE) compared with heterosexual orientation. However, considering that only four studies could be included, the non-probabilistic nature of the samples and the use of different non-standardized indicators of sexual dysfunctions, their results should be interpreted with caution.

The fact is that homosexual individuals have been excluded from a significant number of important clinical trials. When dealing with non-heterosexual people, the investigation of sexuality is hindered by a methodological issue in that most of the questionnaires and diagnostic tools for the assessment of sexual disorders appear to be heterosexual oriented and have not yet been validated for homosexual populations (1).

Authors found that the discussed possible reasons why homosexual men have more chance of suffering with ED and multiple partners (less stability), a sense of competition and what they call: psychological stress - social stigmatization and discrimination against sexual minorities can jeopardize the psychological well-being of homosexuals (2).

The relationship between sexual orientation and ejaculatory function was controversial, since in three studies there is no significant association with sexual orientation. But inside meta-analysis, homosexual men exhibited a 28.0% lower odd of reporting PE compared with heterosexual controls. And is interesting that stable relationship (that was a protective factor in ED) here was a cause of sexual dysfunction. It has been suggested that the higher tendency of heterosexual men to engage in stable relationships might put them at a higher risk for PE compared with gay couples. Jern et al. (3) reported that the ejaculation latency time is negatively correlated to the duration of the relationship.

It is clear that we need more good quality comparative studies using validated tools to identify differences in sexual function/dysfunction among men with others sexual orientations.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

FEMALE UROLOGY

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Editorial Comment: Effect of Behavioral and Pelvic Floor Muscle Therapy Combined With Surgery vs Surgery Alone on Incontinence Symptoms Among Women With Mixed Urinary Incontinence: The ESTEEM Randomized Clinical Trial

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COMMENT

The use of physical therapy has been strongly recommended in the most popular guidelines regarding stress urinary incontinence (1) and overactive bladder (2). In this interesting article published in JAMA, the authors presented a prospective randomized study that sought to evaluate whether performing a mid-urethral sling combined with behavioral therapy and 6 pelvic floor muscle training (PFMT) sessions (n: 209) would yield better outcomes compared to exclusive mid-urethral sling implant (n: 207) in patients with mixed urinary incontinence. Patients were evaluated by the long-form Urogenital Distress Inventory (UDI), and the primary outcome was defined as significant improvement over the baseline condition after 12 months post treatment. In the group that performed the behavioral plus TMAP plus sling, the UDI

score decreased from 178.0 points to 30.7 points (adjusted mean change −128.1 points - 95% CI, −146.5 to −109.8). In the group that was treated by sling alone, the score decreased from 176.8 to 34.5 points (adjusted mean change −114.7 points - 95% CI, −133.3 to −96.2). The model-estimated between-group difference (−13.4 points; 95% CI, −25.9 to −1.0; P = .04) did not meet the minimal clinically important difference threshold. The authors concluded that in women with mixed urinary incontinence, the addition of behavioral and TMAP measures to the mid-urethral sling did not determine clinically relevant changes.

Mixed symptoms represent the majority and most challenging subpopulation among those with incontinence (3). Moreover, even the sling implant can potentially lead to the worsening of storage symptoms in patients with pre-operative mixed urinary incontinence. It is highly unlikely that a unified algorithm could be applicable to all patients, due to the multifactorial origin of the symptoms. Although we agree to the multimodal approach for mixed incontinence, studies that clearly address the cost-effectiveness of combined treatments are still lacking.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

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Editorial Comment: Sacral neuromodulation versus onabotulinumtoxinA for refractory urgency urinary incontinence: impact on fecal incontinence symptoms and sexual function

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COMMENT

The prevalence of double incontinence among Brazilian women is 4.9% and its incidence in the period between 2006 and 2010 was 13.8/1000 person/year (1) In fact, evacuatory and even sexual symptoms are usually underestimated in urological consultations related to overactive bladder (OAB) symptoms. In those women with refractory OAB, the coexistence of these dysfunctions may be even greater. The effects of sacral neuromodulation (SNM) on fecal incontinence are well known, so that this treatment represents an important therapeutic option in double incontinent patients. On the other hand, the therapeutic mechanism of intravesical injection of botulinum toxin (BTX) is much less understood. In this prospective randomized study, the authors performed a post-hoc analysis of data from the ROSETTA trial (2), which included women with refractory urinary incontinence treated with BTX-A (n: 190) or SNM (n: 174). Urinary incontinence and sexual symptoms were evaluated for up to 24 months using the Pelvic Organ Prolapse / Urinary Sexual Incontinence Questionnaire -12 (PISQ-12), IUGA -Revised (PISQ-IR) and St Mark's (Vaizey) Fecal Incontinence Severity Scale. The incidence of fecal incontinence (Vaizey score > 12) did not differ between study groups (BTX: 7.6±5.3 versus SNM: 6.6±4.9, p = 0.07), as did the frequency of sexually active women. Serial evaluations performed after 6, 12, and 24 months post treatment showed improvement of

fecal incontinence in both groups, without significant differences between them in the long-term follow--up. There were no differences between groups in the total PISQ-IR score or any of the PISQ-IR sub--scores in both sexually active and non-sexually active women after 12 months follow-up, although the proportion of sexually active women at the beginning of treatment was almost moderate (BTX: 56% and SNM: 63%, p <0.25).

The effects of BTX on intestinal function are a matter of discussion. Although more evidence is needed, therapeutic effects of BTX may be due to pelvic organ cross-sensitization, as accepted for SNM. Moreover, results from the present study demonstrate the complexity of neurophysiological interactions in the female pelvic floor and also warns about the need for a comprehensive approach to pelvic floor symptoms for a best therapeutic outcome.

CONFLICT OF INTEREST

None declared.

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RADIOLOGY PAGE

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Kidney displaced by giant retroperitoneal liposarcoma in HIV patient

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CASE DESCRIPTION

A 56-year-old male with a history of infection of human immunodeficiency virus over ten years, was referred to our center because of intermittent epigastralgia and gradual increase of abdominal girth in the last two months. Physical examination revealed palpable abdominal mass at the right upper quadrant measuring around 20cm. Laboratory examinations of complete blood counts, urine tests, and tumor markers were otherwise normal. CT scan of the abdomen showed a huge fatty mass of 23.3 x 22.9 x 34.5cm with mixed density and pathological contrast enhancement arising in the retroperitoneum. The mass displaced right kidney in epigastrium (Figure -1A) and most of the bowel away from their natural position in right side of abdomen (Figure-1B). Surgical excision of the mass was performed through a para-midline incision, and revealed a giant clearly encapsulated fatty tumor deriving from the right retroperitoneal fatty tissue (Figure-2A). The mass was completely extirpated without resection of adjacent tissue or organs. The final histopathological report showed a well-differentiated liposarcoma of the retroperitoneum (Figure-2B). The

Figure 1 - A) Right kidney dislocated in epigastrium by the retroperitoneal component of the mass. B) Right colon displaced against abdominal wall and most of the small bowel in left side of abdomen.

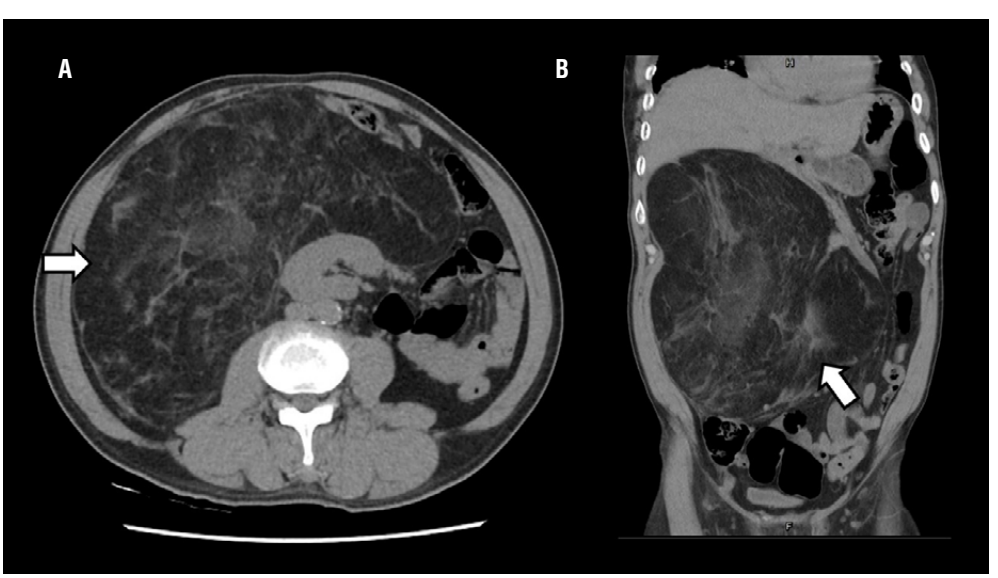
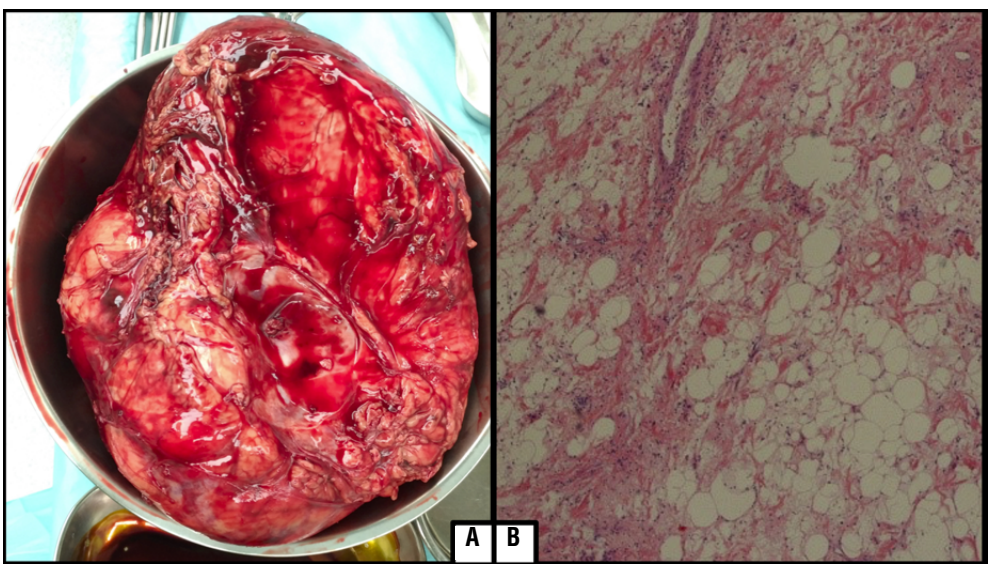


Figure 2 - A) Intraoperative image of the resected specimen. B) Histological examination showed presence of atypical, hyperchromatic stromal cells with a varying number of lipoblasts.



patient's postoperative course was uneventful and he was discharged on the 6th postoperative day. At one year post-surgery, there was no evidence of recurrence on different CT scans.

Retroperitoneum is the primary site in about 15% of soft tissue sarcomas (STS) (1). Liposarcomas account for approximately 40% of retroperitoneal sarcomas making them the most common type (2). The differential diagnoses of masses with retroperitoneal fat content is an usual diagnostic predicament. Computed tomography (CT) imaging features that suggest malignancy include large lesion size, presence of thick septa, presence of nodular and/or globular or non-adipose mass-like areas, and decreased percentage of fat composition (3). Histopathology is central for the distinguishing workup of lipomatous tumors. In the case that lipomalike well differentiated liposarcoma may be hard to discriminate from lipoma, an immunohistochemical panel composed of MDM2 and CDK4 can be useful (4).

Infection with the human immunodeficiency virus (HIV) and the subsequent destruction of T4-positive helper cells are associated with the development of various malignancies.

HIV-infected patients may be at greater risk for other forms of cancer because of changes in immune surveillance. In immunodeficient populations, other than Kaposi sarcoma and other sarcoma types, only leiomyosarcoma and angiosarcoma occur disproportionately in these patients (5). Liposarcomas is usually a malignancy of later life but rare to be encountered in HIV populations. Although it is required to obtain negative resection margins (6), it is necessary to weigh the benefit of free margin resection against the adversity of medical complication in cases where the tumor invades into a nearby organ.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Ambulatory second look percutaneous nephrolithotripsy with maturated nephrostomy tract

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ABSTRACT

Introduction and Objectives: Percutaneous nephrolithotomy (PCNL) is the standard technique for managing large renal calculi. Second-look PCNL is typically performed under intravenous (IV) sedation or spinal / general anesthesia when removing remnant stones. This requires additional pre-anesthesia assessment and close monitoring. To simplify this procedure, we investigated the feasibility and safety of second-look PCNL without anesthesia and sheath after maturation of the nephrostomy tract.

Material and Methods: This study included 14 eligible patients with remnant stones >5mm in diameter, as determined by simple CT scan after supine PCNL through a single nephrostomy tract under general anesthesia. A 24Fr nephrostomy tube was inserted after surgery. Second-look PCNL was performed after seven days of maturation of the nephrostomy tract. Prior to second-look surgery, 25mg pethidine was injected intravenously. Second-look supine PCNL was performed using a rigid or flexible renoscope without anesthesia or sheath.

Results: The mean patient age was 57.4±8.5 years. The mean stone diameter was 5.4 × 3.3cm, while the mean number of stone branches was 4.1±1.4. The mean operation time during the first PCNL was 131.1±24.8 min, and the mean residual stone rate was 24.3%±10.2%. The mean operation time during second-look PCNL was 97.4±36.0 min; after the second procedure, the mean pain score on the numeric rating scale was 2.8±1.0. All patients were stone-free without complications.

Conclusion: Second-look PCNL without anesthesia and sheath after maturation of the nephrostomy tract may be an effective procedure for removing remnant stones in select patients without excessive levels of pain.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Technique of cavoatrial tumor thrombectomy without cardiopulmonary by-pass

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ABSTRACT

Introduction: Open surgery for tumor thrombi in atria is very challenging and are associated with significant morbidity and mortality rates. Here, we explore safety of foleys catheter assisted-technique, obviating the need for open surgery.
Material and Methods: We performed Radical nephrectomy via the midlineincision for renal cell carcinoma with tumor thrombus extending into the right atrium. CTVS team was kept in standby all the time. Intra-operative ECHO was used for monitoring any migration of thrombi into pulmonary. Vessels.
Results: Mean duration of surgery was roughly 4 hours. The time of total IVC occlusion was 2 minutes. The total blood loss was 2350 ml. Intraoperative ECHO showed complete removal of tumor thrombi.
Conclusions: This procedure can be performed in high risk patients with solitary large tumor thrombi.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Retroperitoneoscopic approach for urolithiasis treatment

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ABSTRACT

Objective: To show the main indications of retroperitoneoscopy (RP) for the treatment of urolithiasis. The use of RP approach has been limited, being narrow working space the major issue to overcome (1), especially in non-expert hands. However, RP has the added advantages of no peritoneal contamination, a quick recovery of bowel function (2) and the possibility to use it in combination with other endourological techniques (3) and innovative technology.
Materials and Methods: We performed a retrospective analysis of 22 patients treated by the retroperitoneoscopic approach due to urolithiasis disease between 2015-2017. Type of surgery, stone free rate (SFR), complications according to Clavien-Dindo classification and mean hospital stay were recorded. Radical and partial nephrectomy cases were excluded for the SFR calculation. Descriptive statistical analysis was done using SPSS v21.
Results: Of the 22 patients treated by the retroperitoneoscopic approach, 9 underwent a ureterolithotomy, 4 underwent a nephrolithotomy, 8 were nephrectomies and 1 was a polar nephrectomy. In 3 cases we used the indocianine green fluorescence (ICG) to find avascular planes, reduce the bleeding, permitting enhanced visualization and reconstruction. In 3 cases an additional percutaneous approach was used, increasing the SFR chances. Eleven of thirteen (84.6%) patients were stone free following the procedure. Tree complications were recorded, two Clavien II and one Clavien III complications. Mean hospital stay was 4 days.
Conclusions: Retroperitoneoscopic approach is a good alternative for the treatment of large impacted ureteral stones, large pielic stones and for non-functional kidney removal due to stone disease. In expert hands, it can be safely used with a good SFR. The combination with ICG or other endourological techniques is feasible, allowing higher SFR.

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CONFLICT OF INTEREST

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VIDEO SECTION

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Single port robot-assisted transperitoneal kidney transplant using the SP® surgical system in a pre-clinical model

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ABSTRACT

Introduction: Minimally invasive surgery has recently gained interest for kidney transplantation. We aimed to describe the step-by-step technique for single-port robotic transperitoneal kidney transplantation using the SP® surgical system (Intuitive Surgical, Sunnyvale, Ca) in a pre-clinical model.
Materials and Methods: A male fresh cadaver model was placed in a lithotomy position. A 3cm midline incision was made 4cm cephalad to the belly button. An advanced access platform (GelPOINT, Rancho Margarita, California, USA) was inserted into the abdominal cavity through the incision. A left kidney was obtained for the local procurement organization. Bench preparation of the kidney was performed. Thereafter, the organ was introduced transperitoneal through the Alexis® wound retractor. The SP® robotic platform was docked and the pelvic fossa was targeted. The standardized steps of robotic multi-arm kidney transplant were duplicated. Primary outcomes such as intraoperative complications, rate of conversion to standard technique and operative times were recorded.
Results: The procedure was technically completed using the SP® robotic system without conversion or the need for additional ports. There were no intraoperative complications. The total operative time was 182 minutes, with 35 minutes spent for bench kidney.
Conclusions: Robotic Single-Port kidney transplantation using the SP® surgical platform is feasible in a pre-clinical model. The platform could be particularly interesting for multi-quadrant surgery such as auto-transplantation, potentially reducing the time for redocking. Further clinical studies in humans and comparison with standard surgical techniques are warranted.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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Re: Reflections on the COVID-19 Pandemic

Riccardo Bertolo [1], Cipriani Chiara [1], Vittori Matteo [1], Bove Pierluigi [1, 2]

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To the editor,

We all know that Coronavirus disease 2019 (COVID-19) has been declared a pandemic on March 11th, 2020. Such dramatic scenario deeply impacted on the healthcare systems worldwide.

If telemedicine allows for the remote provision of healthcare by means of electronic communication tools in case of medical conditions, surgical indications could be not deferrable (1, 2).

Major surgical societies have been prompted in publishing position papers and guidelines for best surgical practice. Among these, the European Association of Urology (EAU) Robotic Urology Section (ERUS) recently published its Guidelines on dealing with robotic surgery in the COVID-19 era (3).

Such guidelines include behavioral good clinical practice rules aimed to maximize the safety and the protection against COVID-19 for both patients and healthcare professionals involved in the robotic surgical activity. We followed the principles included in the ERUS guidelines either for pure-laparoscopic or robot-assisted procedures performed at our Institution since the beginning of the COVID-19 crisis. All patients with indication to surgery received preoperative health screening, with none of them reporting symptoms suggestive for COVID-19. Procedures were performed in a dedicated operative room. All the necessary protection tools and general recommendations to reduce the transmission of the disease were adequately followed (3). Selection of indications was considered in order to minimize the number of medical personnel involved and the expenditure of medical equipment. As such, only cystectomies, prostatectomies for high risk disease and renal surgeries for large renal masses were performed. All elective surgeries that could be delayed without any risk for the patient were postponed. Listed laparoscopic surgeries were performed at the lowest intra-abdominal pressure possible (8-10 mmHg), by using an intelligent integrated flow system (AirSeal®, ConMed, Utica, NY), allowing for system-assisted desufflation of the pneumoperitoneum. The minimum number of operative room staff members was adopted. No external observers, including residents and/or fellows, were allowed. Standardized surgical techniques were performed by experienced surgeons, in order to reduce the operative time and the risk of complications.

At the end of a three-weeks period, the teams involved in the operative room setting (including surgeons, anesthetists, nurses, operative room housekeepers and patients' porters) were screened with a COVID-19 IgM/IgG rapid test lateral flow immunoassay, nowadays validated for the rapid diagnosis of COVID-19 (4).

VivaDiagTM COVID-19 IgM/IgG was performed according to the manufacturer's instruction (5). After 15 minutes about, the result was read. Overall, > 300 tests were performed at our Institution. We focused on the 85 professionals who were related with the operative room activities reported herein. None of them resulted positive for either active or previous infection.

To date, real-time polymerase chain reaction in respiratory samples is the gold standard method for diagnosing COVID-19 (6). Nevertheless, molecular tests are time consuming, requiring specialized operators, thus limiting widespread use in real-life.

This is why we adopted VivaDiagTM COVID-19 IgM/IgG test. Although sensitivity has been published to be low (4,5), specificity is around 92%.

At a price running to 10 euros per person screened, we believe it could represent a value-for-money passport for immunity of health-care professionals.

ACKNOWLEDGEMENTS

To the president Ettore Sansavini, who offered the health-care professionals of San Carlo di Nancy Hospital, Rome, to undergo the test.

CONFLICT OF INTEREST

None declared.

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