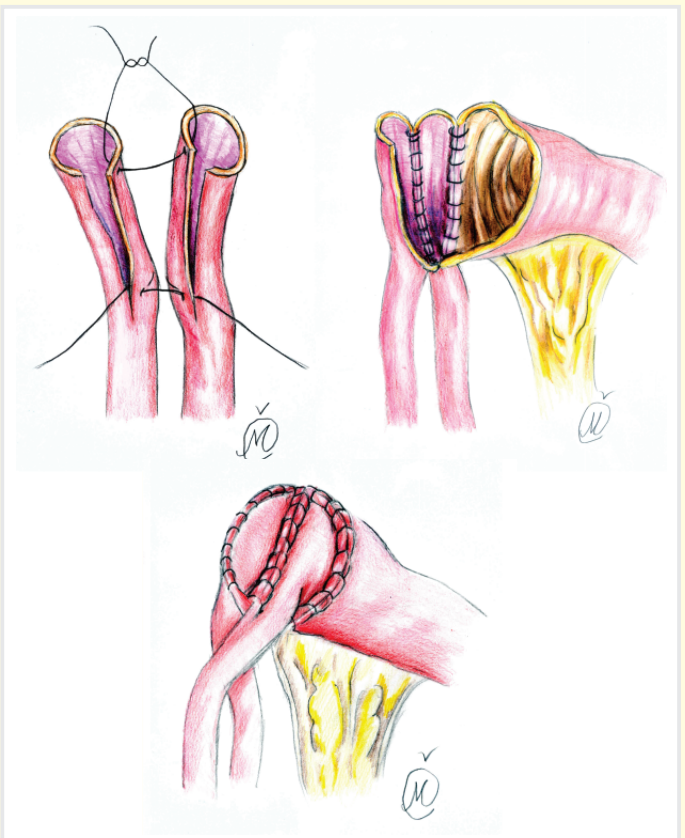
ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY
VOLUME 46, NUMBER 3, MAY - JUNE, 2020



Ureters were spatulated and sutured together with continuous 4-0 Vicryl suture, while the lateral edges of the newly conjoined ureters were anastomosed to the proximal end of an open ileal conduit segment, using 4-0 PDS interrupted suture, according to the standard Wallace I technique. (*page 449*).

SOCIEDADE BRASILEIRA DE UROLOGIA

XXXVIII Brazilian Congress of Urology
August 28 - 31, 2021 - Brasilia - DF - Brazil

INTERNATIONAL

BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY - SBU

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

CONSULTING EDITORS

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL

BRAZ J UROL

Eletronic Version: Full text with fully searchable articles on-line:

https://www.intbrazjurol.com.br

Correspondence and Editorial Address:

Rua Real Grandeza, 108 - conj. 101 - 22281-034 – Rio de Janeiro – RJ – Brazil
Tel.: + 55 21 2246-4003; E-mail: brazjurol@brazjurol.com.br

The paper on which the International Braz J Urol is printed meets the requirements of ANSI/NISO Z39, 48-1992 (Permanence of Paper). Printed on acid-free paper.

The International Braz J Urol is partially supported by the Ministry of Science and Technology. National Council for Scientific and Technological Development.
Editorial and Graphic Composition

The International Braz J Urol, ISSN: 1677-5538 (printed version) and ISSN: 1677-6119 (electronic version) is the Official Journal of the Brazilian Society of Urology– SBU, is published 6 times a year (bimonthly, starting in January - February).

The International Braz J Urol is indexed by: EMBASE/Excerpta Medica; SciELO, Lilacs/Latin America Index; Free Medical Journals; MD-Linx; Catálogo Latindex; SCImago, Index Medicus - NLM, PubMed/MEDLINE, PubMed/Central, ISI - Current Contents / Clinical Medicine and Science Citation Index Expanded.

ONLINE manuscript submission: **www.intbrazjurol.com.br**

DISCLAIMER

CONTENTS

Volume 46 | number 3 | May . June, 2020 | INT BRAZ J UROL

EDITORIAL IN THIS ISSUE

REVIEW ARTICLE

ORIGINAL ARTICLE

Male Health

Prostate Cancer

Female Urology

Renal Cancer

RADIOLOGY PAGE

VIDEO SECTION

EDITORIAL
IN THIS ISSUE

Vol. 46 (3): 311-313, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.01

Pediatric Urology highlighted

Luciano A. Favorito [1, 2]

[1] Unidade de Pesquisa Urogenital - Universidade do Estado de Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil, [2] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil

The May-June number of *Int Braz J Urol,* the 3rd under my supervision, presents original contributions with a lot of interesting papers in different fields: Prostate Cancer, Renal Cell Carcinoma, Penile trauma, Bladder Cancer, Neurogenic Bladder, Robotics, Laparoscopy, Male Health, Ureteroscopy, Hypospadia, Urinary diversion and Testicular Cancer. The papers came from many different countries such as Brazil, USA, Turkey, China, Montenegro, Spain, India and Italy, and as usual the editor´s comment highlights some of them. Pediatric urology is the highlight of this number. In the present issue we present two important reviews: in page 314 Dr. Kirsch and Arlen from Atlanta - USA (1) review in a nice narrative if the open ureteral reimplantation is still the gold standard treatment in surgical management of vesicoureteral reflux and the authors concluded that open, laparoscopic/robot- assisted and endoscopic approaches are all successful in correcting re ux and have been shown to reduce the incidence of febrile urinary tract infections and Dr. Fuchs and Dajusta and from Columbus – USA (2) present in page 322 an important review about robotics in Pediatric urology and concluded that several procedures in Robotic has also shown feasibility and comparable success when compared to open surgery in procedures that were previously deemed too complex to be done by standard laparoscopy.

Dr. Azambuja and collegues from Brazil performed on page 353 (3) an important retrospective study about the treatment of testicular cancer with platinum combinations in 50 patients. The authors concluded that the expression of excision repair cross-complementation (ERCC1) and nuclear factor kappa-B give a worse prognosis for relapse, and only ERCC1 had an influence on the overall survival of Testicular germ cells tumor patients treated with platinum-based chemotherapy. These may represent markers that predict poor clinical outcome and response to cisplatin.

Dr. Sharma and Collegues from India performed on page 363 (4) a very important study about the use of androgen deprivation therapy (ADT) in carcinoma prostate (CaP) and if the ADT has deleterious effect on bone mineral density (BMD) leading to increase incidence of osteoporosis and skeletal-related events in 96 patients and concluded that the Bone-directed therapy (Zoledronic acid) leads to both subjective and objective improvement in bone health of prostate cancer patients on ADT.

Dr. Taha and collegues from Brazil studied patients over 60 years of age, to obtain data on its sexual and urinary health with 3425 questionnaires and found a large number of sexual and urinary disorders and recommended the improvement in health conditions, promoting a better quality of life in the elderly (5).

Dr. Freitas and collegues from Brazil performed on page 383 (6) another study about Androgen deprivation therapy (ADT) in advanced prostate cancer and compared efficacy of three schedules of

leuprolide acetate in lowering PSA in a real world population in 932 patients during 11 years and concluded that PSA levels can be effectively be reduced in most patients treated with monthly, quarterly, or semiannual injections of long-acting leuprolide acetate.

Dr. Fedrigon and Collegues from USA performed on page 390 (7) a in vitro study about two automated irrigation systems for use during ureteroscopy and concluded that each system provided steady irrigation at safe pressures within their expected operating parameters with small differences in performance that should not limit their ability to provide steady irrigation at safe pressures.

Dr. Barros and Collegues from Rio de Janeiro- Brazil demonstrated in page 409 (8) in a very nice paper the experience over the past 20 years in the diagnosis and surgical treatment of penile fracture (PF) in 255 patients and concluded that penile fracture has typical clinical presentation and no need for additional tests in most cases. The 'doggy style' and 'man-on-top' was the most common positions and generally associated with more severe lesions. Concomitant urethral injury should be considered in cases of high-energy trauma. Surgical reconstruction produces satisfactory results, however, it can lead to complications, such as erectile dysfunction and penile curvature.

Dr. Kalil and Dr. D'ancona in page 419 (9) in a very important paper evaluated the lower urinary tract symptoms, classified by the International Prostate Symptom Score (IPSS), urodynamic results, Watts Factor (WF), Bladder Contractility Index (BCI), and post void residual (PVR), in order to differentiate Detru- sor Underactivity (DU) from Bladder Outlet Obstruction (BOO) in 44 patients and concluded that isolated symptoms, classified by IPSS and PVR, could not differentiate patients with DU from those with BOO, but it was possible using urodynamic data.

Finally, Dr. Kavaric and Collegues from Montenegro performed on page 446 (10) the study that is on the cover in this number. The authors compared perioperative outcomes, complications and anastomotic stricture rate in a contemporary series of patients who underwent open radical cystectomy (RC) with modified Wallace anastomotic technique versus traditional ileal conduit in 140 randomized patients and concluded that the use of the modified Wallace technique leaves to significantly lower anastomotic stricture and anastomotic leakage rates, which are major issues in minimizing both short and long-term postoperative complications.

We hope that readers will enjoy the present number of the *International Brazilian Journal of Urology.*

REFERENCES

1. Kirsch AJ, Arlen AM. Evolving surgical management of pediatric vesicoureteral reflux: is open ureteral reimplantation still the 'Gold Standard'? Int Braz J Urol. 2020;46:314-21.
2. Fuchs ME, DaJusta DG. Robotics in Pediatric Urology. Int Braz J Urol. 2020;46:322-7.
3. Azambuja AA, Engroff P, Silva BT, Zorzetti RCS, Morrone FB. Evaluation of nuclear NF-κB, transglutaminase2, and ERCC1 as predictors of platinum resistance in testicular tumors. Int Braz J Urol. 2020;46:353-62.
4. Sharma A, Sinha RJ, Garg G, Agarwal S, Statistician AA, Singh V. Special emphasis on bone health management in prostate cancer patients: a prospective longitudinal study. Int Braz J Urol. 2020;46:363-73.
5. Taha KA, Rocha FT, Castilho L. Profile of sexuality and symptoms of lower urinary tract in non-institutionalized elderly. Int Braz J Urol. 2020;46:374-80.
6. de Freitas CSM, Soares AN. Efficacy of Leuprorelide acetate (Eligard®) in daily practice in Brazil: a retrospective study with depot formulations in patients with prostate cancer. Int Braz J Urol. 2020;46:383-9.
7. Fedrigon D III, Alshara L, Monga M. Comparison of automated irrigation systems using an in vitro ureteroscopy model. Int Braz J Urol. 2020;46:390-7.
8. Barros R, Hampl D, Cavalcanti AG, Favorito LA, Koifman L. Lessons learned after 20 years' experience with penile fracture. Int Braz J Urol. 2020;46:409-16.
9. Kalil J, D Ancona CAL. Detrusor underactivity versus bladder outlet obstruction clinical and urodynamic factors. Int Braz J Urol. 2020;46:419-24.
10. Kavaric P, Eldin S, Nenad R, Dragan P, Vukovic M. Modified wallace anastomotic technique reduces ureteroenteric stricture rates after ileal conduit urinary diversion. Int Braz J Urol. 2020;46:446-55.

Luciano A. Favorito, MD, PhD

Unidade de Pesquisa Urogenital
da Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

ARTICLE INFO

Luciano A. Favorito
http://orcid.org/0000-0003-1562-6068

Int Braz J Urol. 2020; 46: 311-3

REVIEW ARTICLE

Vol. 46 (3): 314-321, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.99.05

Evolving surgical management of pediatric vesicoureteral reflux: is open ureteral reimplantation still the 'Gold Standard'?

Andrew J. Kirsch [1], Angela M. Arlen [2]

[1] *Emory University School of Medicine Children's Healthcare of Atlanta, Atlanta, GA 30328, USA;*
[2] *Department of Urology, Yale University School of Medicine, New Haven, CT 06520, USA*

ABSTRACT

Vesicoureteral reflux, the retrograde flow of urine from the bladder into the upper urinary tract, is one of the most common urologic diagnoses in the pediatric population. Once detected, therapeutic options for urinary reflux are diverse, ranging from observation with or without continuous low-dose prophylactic antibiotics to a variety of operative interventions. While a standardized algorithm is lacking, it is generally accepted that management be tailored to individual patients based on various factors including age, likelihood of spontaneous resolution, risk of subsequent urinary tract infections with renal parenchymal injury, and parental preference. Anti-reflux surgery may be necessary in children with persistent reflux, renal scarring or recurrent pyelonephritis after optimization of bladder and bowel habits. Open, laparoscopic/robot-assisted and endoscopic approaches are all successful in correcting reflux and have been shown to reduce the incidence of febrile urinary tract infections.

ARTICLE INFO


Angela M. Arlen
http://orcid.org/0000-0002-4921-6342

Keywords:
Vesico-Ureteral Reflux; Ureteral Diseases; Pediatrics

Int Braz J Urol. 2020; 46: 314-21

Submitted for publication:
January 04, 2020

Accepted after revision:
January 10, 2020

Published as Ahead of Print:
January 20, 2020

INTRODUCTION

Vesicoureteral reflux (VUR) is one of the most common urologic diagnoses affecting children, with an estimated prevalence of 0.4-1.8% in the general pediatric population, 10-20% of those with antenatal hydronephrosis, and up to 40% of children with a history of febrile urinary tract infection (UTI) (1-3). Moreover, newborns have a higher propensity for renal injury and are at higher risk of having VUR after initial febrile UTI (4). Management options for urinary reflux encompass a broad spectrum, ranging from observation with or without continuous low-dose antibiotic prophylaxis to a variety of operative interventions. In recent years, aggressive reflux management has been called into question and a more selective approach to the diagnosis and treatment of VUR

has gained favor, with an emphasis on identifying children at risk for recurrent pyelonephritis and renal scarring (5, 6).

Successful surgical correction of VUR in children can be achieved via open, laparoscopic or robot-assisted laparoscopic or endoscopic approaches and fortunately for pediatric urologists and surgeons, all are potentially successful and have their merits. The decision *how to best* surgically manage primary VUR is dependent on a multitude of factors, including the influence of training and personal experience of the surgeon, and the impact of published literature. Biases exist in data reporting and selective data use, as well as potential economic benefits to the surgeon using one approach over another. Ideally, after careful consideration of the various pros and cons of each approach, shared decision-making between the family and the surgeon will lead to the most appropriate intervention for a given patient.

Open ureteral reimplantation (OUR), robot-assisted laparoscopic extravesical reimplantation (RALUR), and endoscopic injection (EI) have all proven effective at correcting VUR and preventing febrile urinary tract infections (7, 8). Defining "success" postoperatively is key to comparing the outcomes of each surgical procedure and analyzing available literature. This review will emphasize how implementation of an individualized care model, taking into consideration current data on the benefits and complications of anti-reflux surgery, is leading to the emergence of new "gold standards" in the surgical management of VUR. Today, the "gold standard" surgical approach must result in a reduction of febrile UTIs, have low morbidity and be reproducible, while also being acceptable to parents of children with VUR.

How is "Success" of Anti-Reflux Surgery Defined?

Management goals of VUR include prevention of recurrent pyelonephritis and renal injury while minimizing the morbidity of associated treatment and follow-up (9). Surgical success can be defined both radiographically (i.e. no VUR on postoperative voiding cystogram) and clinically (i.e. no postoperative febrile UTIs) (10). Arguably the prevention of recurrent febrile UTIs, the very reason for obtaining a VCUG and diagnosing VUR in the first place, should be considered the *primary* definition of success and thus more important in the long term than radiographic findings. The clinical definition of success also underscores the importance of screening for and treatment of bladder-bowel dysfunction (BBD) prior to any anti-reflux procedure, as dysfunctional elimination influences not only surgical success but the risk of febrile UTI (9).

Open Ureteral Reimplantation

Creation of a ureteroneocystostomy is an elegant surgical skill that has helped to define the field of pediatric urology for over 50 years, and various open reimplantation techniques have been described including both intravesical and extravesical approaches. The Cohen cross-trigonal reimplantation is the most widely utilized intravesical ureteroneocystostomy technique, due to reliable results and broad applicability. It maintains the same ureteral hiatus in the bladder wall, with the ureter advanced through a submucosal tunnel across the trigone to the contralateral bladder wall (11-13). It is well-suited for small or thick-walled bladders, as ureteral advancement across the back wall of the bladder rarely results in kinking or obstruction. The technique utilized for extravesical ureteral reimplantation is the Lich-Gregoir or one of its modifications. In this approach, the juxtavesical ureter is dissected free but not detached and a detrusor trough is created by incising the serosa and detrusor down to the mucosa, extending laterally from the ureteral hiatus. The refluxing ureter is placed into the trough, and the detrusor is closed over the ureter, creating a flap valve mechanism without opening the bladder (14, 15).

The idiom "tried-and-true" describes OUR perfectly as it has long been touted as the "gold standard" with radiographic success rates reported to be up to 98% for grades I-IV. Given this high success rate, the need for a routine postoperative VCUG is usually dictated by the patient's postoperative clinical course and is not routinely recommended (9). Despite being regarded as the gold standard, there is surprisingly limited recent literature describing the long-term clinical outcomes after open reimplantation. The International Reflux Study in Children reported a 5-year UTI incidence

of 39% following surgery for dilating reflux (grade III-V), while clinical pyelonephritis occurred in 10% (16). In 2013, Nelson et al. published a large series of over 1000 children undergoing OUR, with radiographic success achieved in 93.5% (96.5% in those without ureteral tailoring). During a median follow-up of 2.9 years, 6.5% of children developed clinical pyelonephritis while the incidence of any postoperative UTI was 21.8% (17). This underscores the need to counsel caregivers that while OUR is successful at correcting VUR and therefore preventing pyelonephritis, postoperative UTI remains relatively common. As anticipated, failure was higher in girls, those with renal scarring, higher VUR grade, and in those with increased number of preoperative UTIs. Furthermore, the morbidity as measured by emergency room visits and hospitalizations postoperatively is notably higher when OUR is compared to EI (18). These findings underscore the reality that OUR may not be superior to either EI or RALUR with regards to clinical outcomes rather, it is one of several surgical options for correcting primary VUR.

Robot-Assisted Laparoscopic Ureteral Reimplantation

Use of minimally invasive surgical techniques has become increasingly common in the pediatric population over the past decade, and robotic technology has served to bridge the gap between open and laparoscopic surgery with magnified three-dimensionality and superior stereoscopic visualization (19, 20). Given the need for delicate intracorporeal suturing, robotic surgery is particularly advantageous for reconstructive procedures (21, 22). Robotic reimplantation is typically performed via an extravesical approach and has gained increasing acceptance (19, 23).

VUR resolution rates after extravesical robotic ureteral reimplantation reported in the literature range from 66.7 to 100% in multiple relatively small series; the overall radiographic success rate upon pooling these series is 91% (24). A multi-institutional retrospective study reported radiographic success of 87.9%; Clavien grade III and lower complications were seen in fewer than 10%, including 3.9% of cases with transient acute urinary retention after bilateral RALUR, a known complication of bilateral extravesical reimplantation (25). The same consortium of robotic surgeons then conducted a prospective multicenter study on RALUR, and reported a slightly higher resolution rate of 93.8% with a 91.9% clinical success rate (8.1% incidence of postoperative febrile UTI) (26).

In comparison to OUR, RALUR has been associated with decreased morbidity, less postoperative pain, lower analgesic requirements, quicker postoperative recovery, and shorter hospital stays. However, there are multiple reports of higher complication rates with the robotic compared to the open approach and while success rates approach that of OUR (27, 28), shared decision making with caregivers helps determine the best approach for an individual child. As with other robot-assisted laparoscopic operations, advantages compared to an open approach seem most apparent in older children and must be balanced against operative time and cost considerations. Furthermore, evidence suggests that a hidden Pfannenstiel incision may be more desirable than visible port sites used in the robotic approach (29). While multi-institutional studies support RALUR as a safe and effective treatment option in older patients when performed by experienced surgeons (25, 26), efforts to identify patient and technique factors associated with optimal surgical outcomes while minimizing complications remains key.

Endoscopic Injection

Endoscopic correction using an injectable bulking agent as an alternative to open anti-reflux surgery was initially described nearly four decades ago. O'Donnell and Puri popularized the concept by performing subureteric injections using Teflon paste, i.e the "STING" (subureteric teflon injection) procedure (30). Double hydrodistention implantation technique (Double HIT), the hallmark of which is ureteral hydrodistention, allows for direct visualization and injection into the intraluminal ureteral submucosal plane and improved success rates (31). In the Double HIT method, the needle is placed into the distended ureteral orifice and inserted in the mid-ureteral tunnel at the 6 o'clock position (rather than below the orifice as with the STING technique). Dx/HA is injected until a sufficient bulge is produced, coapting the detrusor

tunnel. The second injection at the distal most aspect of the intravesical ureteral tunnel results in coaptation of the ureteral orifice. Hydrodistention, with the bladder nearly empty, is performed following each injection to monitor progress and ensure adequate ureteral coaptation (32).

Proponents of the endoscopic approach tout benefits including the ambulatory nature and decreased patient morbidity, while opponents note both higher initial radiographic failure and recurrence rates compared to ureteral reimplantation. Success rates of up to 94% have been reported by our group with the Double HIT methods (10, 33, 34). Other studies using varying techniques and injected volumes, have demonstrated wide variability with reported treatment failure rates of 6-50%; outcomes are dependent upon the technique utilized, injected material, VUR grade and surgeon experience (35). Aggregate literature suggests that endoscopic therapy is relatively effective for the treatment of most primary VUR, while stressing the importance of reflux grade and structural/functional bladder anomalies on ultimate success rates. In a systematic meta-analysis evaluating Dx/HA for pediatric VUR, the estimated overall reported success rate for endoscopic therapy was 72% with 89% success for grade I, 83% for grade II, 71% for grade III, 59% for IV and 62% for grade V reflux (36). It is important to re-emphasize that this meta-analysis included various injection methods, volumes of injected material, and surgeon experience. Despite the potential for lower radiographic success rates, families and surgeons alike are drawn EI, due to the minimally invasive nature and similar clinical success. In some studies using the STING technique and relatively lower volume of injection, length of follow-up has had an impact on EI success rates. Radiographic recurrence of reflux after initial successful STING injection appears to be around 15-20% within several years and is stable thereafter (37-39). Late radiographic failures are hypothesized to be secondary to the biodegradable nature of Dx/HA; the clinical significance of late recurrent VUR in the absence of symptomatic infections is unclear, however, down-grading VUR may play an important role.

Our experience using Dx/HA over nearly twenty years has been quite good with outcomes similar to that reported for OUR and RALUR. In a series of 229 children undergoing EI with Dx/HA, 14 patients (6.3%) experienced a postoperative febrile UTI during mean clinical follow-up of 34.7 months (33). In a longer-term study with greater than 5-year (median 8.4 year) follow-up, a 10.2% incidence of postoperative febrile UTI was reported (40). These studies underscore the long-term clinical success rate of Double HIT for primary VUR. We no longer suggest VCUGs following EI since studies have confirmed no benefit to those patients who have undergone a postop VCUG compared to those who have not (33).

The biodegradable nature of the Dx/HA copolymer and its role in long-term failures prompted development of the synthetic, non-biodegradable Polyacrylate Polyalcohol Copolymer (PPC, Vantris®) (41). PPC has had promising short and long-term results outside of the United States since its introduction in 2010 (42). In a comparative study, Warchol and colleagues reported considerably higher success rates after a single injection with PPC compared to Dx/HA (43). These findings were confirmed in a recently published study, which reported a PPC radiographic success rate of 92.2% compared to 75.7% for Dx/HA, controlling for grade and injection technique (44). Studies have indicated a higher complication rate, notably ureteral obstruction, using PPC. As a result, most agree that the Double HIT method should not be used with PPC.

What Do Patients and Parents Prefer?

Shared decision making, the collaborative process of clinicians and patients (or parental surrogates) making medical decisions together, takes into consideration not only risks and benefits of a given intervention, but also the preferences, goals, and concerns of the family before arriving at a decision (45). Perhaps nowhere is this concept more relevant in pediatric urology than in diagnoses of primary VUR, where 'optimal' treatment remains heavily debated and a universal management algorithm is lacking. Furthermore, the clinical success rates of OUR, RALUR and EI are all similar, underscoring the

merits of each approach and the need for individualized care (Figure-1). In summary, what may be ideal for one child may not be the "gold standard" for another.

In 2011, the American Academy of Pediatrics (AAP) revised the practice parameters regarding diagnosis and management of initial febrile UTIs in infants and young children aged 2 to 24 months; guidelines now recommend that children with initial febrile UTI undergo a renal--bladder ultrasound, but forego VCUG unless indicated by sonographic findings (i.e. hydronephrosis, scarring) (5). The revised guidelines challenge the utility of aggressive diagnosis and subsequent management of *all* primary reflux, representing a shift towards a more selective approach. Not surprisingly, national trends in the surgical management of primary reflux in children have revealed significant declines in OUR and EI since the publication of the revised AAP UTI guidelines (46). However, OUR has been on a statistically significant decline well before guideline publication, showing a downward trend since before 2004. Accounting for this shift was the emergence of EI in the USA in 2001. Since 2008, RALUR has shown a modest rise in utilization further competing with OUR. It is difficult to discern the role that parental preference plays in these trends, but the decline of open surgical repairs, may suggest that families and clinicians are opting for more minimally invasive options.

CONCLUSIONS

Over the past decade, there has been a shift towards a more selective approach to surgical management of primary urinary reflux, aimed at identifying children most likely to experience the untoward effects of recurrent pyelonephritis who would therefore benefit from surgical repair. While open ureteroneocystostomy, robot-assisted laparoscopic reimplantation, and endoscopic injection have differing ranges of reported radiographic success, it is important to note their rates of clinical success are similar. If the ultimate goal is prevention of febrile urinary tract infections, we must also acknowledge a shift in what is considered the "gold standard" in operative management of VUR. Based on our experience and that reported by others, we include our surgical treatment algorithm (Figure-2), emphasizing that there are several "gold standards" from which to optimize the care of an individual child with primary VUR.

Figure 1 - Comparison of clinical and radiographic success of open ureteral reimplantation (14), robotic ureteral reimplantation (26) and Dx/HA injection (33).

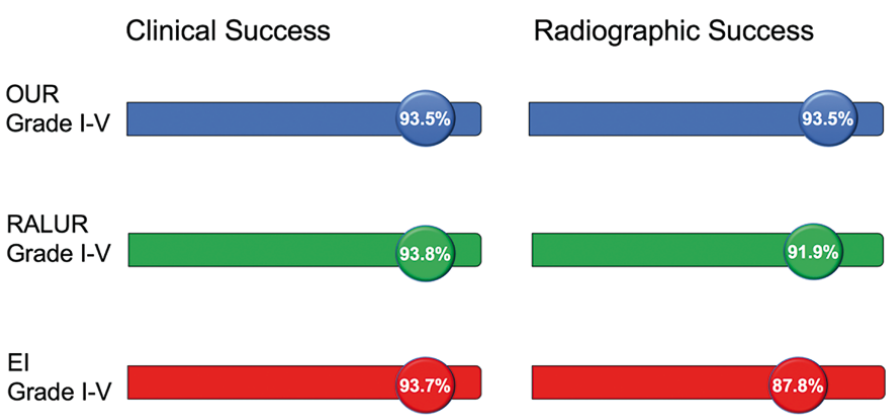
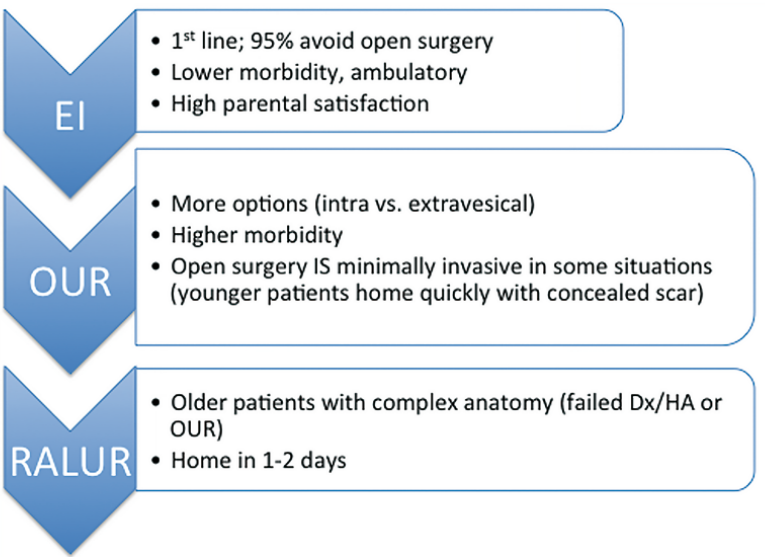


Figure 2 - EI may be considered first line surgical therapy for most cases of grade II-IV VUR, owing to its ambulatory nature and good clinical success. OUR offers more approaches with high radiographic and clinical success rates, but higher morbidity compared to EI must be considered. RALUR is an option in older children but is typically limited to an extravesical approach.



CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sargent MA. What is the normal prevalence of vesicoureteral reflux? Pediatr Radiol. 2000;30:587-93.
2. Skoog SJ, Peters CA, Arant BS Jr, Copp HL, Elder JS, Hudson RG, et al. Pediatric Vesicoureteral Reflux Guidelines Panel Summary Report: Clinical Practice Guidelines for Screening Siblings of Children With Vesicoureteral Reflux and Neonates/Infants With Prenatal Hydronephrosis. J Urol. 2010;184:1145-51. Erratum in: J Urol. 2011;185:365.
3. Nguyen HT, Herndon CD, Cooper C, Gatti J, Kirsch A, Kokorowski P, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol. 2010;6:212-31.
4. Pokrajac D, Sefic-Pasic I, Begic A. Vesicoureteral Reflux and Renal Scarring in Infants After the First Febrile Urinary Tract Infection. Med Arch. 2018;72:272-5.
5. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011;128:595-610.
6. Bandari J, Docimo SG. Vesicoureteral reflux is a phenotype, not a disease: A population-centered approach to pediatric urinary tract infection. J Pediatr Urol. 2017;13:378-82.
7. Boysen WR, Akhavan A, Ko J, Ellison JS, Lendvay TS, Huang J, et al. Prospective multicenter study on robot-assisted laparoscopic extravesical ureteral reimplantation (RALUR-EV): Outcomes and complications. J Pediatr Urol. 2018;14:262.e1-262.e6.
8. Lightfoot M, Bilgutay AN, Tollin N, Eisenberg S, Weiser J, Bryan L, et al. Long-Term Clinical Outcomes and Parental Satisfaction After Dextranomer/Hyaluronic Acid (Dx/HA) Injection for Primary Vesicoureteral Reflux. Front Pediatr. 2019 27;7:392.
9. Peters CA, Skoog SJ, Arant BS Jr, Copp HL, Elder JS, Hudson RG, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol. 2010;184:1134-44.
10. Kaye JD, Srinivasan AK, Delaney C, Cerwinka WH, Elmore JM, Scherz HC, et al. Clinical and radiographic results of endoscopic injection for vesicoureteral reflux: defining measures of success. J Pediatr Urol. 2012;8:297-303.
11. Cohen SJ. Ureterozystoneostomie: Eine neue antireflux Technik. Aktuelle Urol 1975;6:1.
12. Retik AB, Colodny AH, Bauer SB. Genitourinary surgery. Pediatric Urology.1984;2:764.
13. Sung J, Skoog S. Surgical management of vesicoureteral reflux in children. Pediatr Nephrol. 2012;27:551-61.

14. Lich R, Jr., Howerton LW, Davis LA. Recurrent urosepsis in children. J Urol 1961;86:554-8.
15. Gregoir W, vanregemorter G. Congenital vesico-ureteral reflux. Urol Int. 1964;18:122-36.
16. Jodal U, Koskimies O, Hanson E, Löhr G, Olbing H, Smellie J, et al. Infection pattern in children with vesicoureteral reflux randomly allocated to operation or long-term antibacterial prophylaxis. The International Reflux Study in Children. J Urol. 1992;148(5 Pt 2):1650-2.
17. Nelson CP, Hubert KC, Kokorowski PJ, Huang L, Prasad MM, Rosoklija I, et al. Long-term incidence of urinary tract infection after ureteral reimplantation for primary vesicoureteral reflux. J Pediatr Urol. 2013;9:92-8.
18. Wang HS, Tejwani R, Wolf S, Wiener JS, Routh JC. Readmissions, unplanned emergency room visits, and surgical retreatment rates after anti-reflux procedures. J Pediatr Urol. 2017;13:507.e1-507.e7.
19. Gundeti MS, Kojima Y, Haga N, Kiriluk K. Robotic-assisted laparoscopic reconstructive surgery in the lower urinary tract. Curr Urol Rep. 2013;14:333-41.
20. Arlen AM, Kirsch AJ. Recent Developments in the Use of Robotic Technology in Pediatric Urology. Expert Rev Med Devices. 2016;13:171-8.
21. Van Batavia JP, Casale P. Robotic surgery in pediatric urology. Curr Urol Rep. 2014;15:402.
22. Bilgutay AN, Kirsch AJ. Robotic Ureteral Reconstruction in the Pediatric Population. Front Pediatr. 2019;7:85.
23. Marchini GS, Hong YK, Minnillo BJ, Diamond DA, Houck CS, Meier PM, et al. Robotic assisted laparoscopic ureteral reimplantation in children: case matched comparative study with open surgical approach. J Urol. 2011;185:1870-5.
24. Akhavan A, Avery D, Lendvay TS. Robot-assisted extravesical ureteral reimplantation: outcomes and conclusions from 78 ureters. J Pediatr Urol. 2014;10:864-8.
25. Grimsby GM, Dwyer ME, Jacobs MA, Ost MC, Schneck FX, Cannon GM, et al. Multi-institutional review of outcomes of robot-assisted laparoscopic extravesical ureteral reimplantation. J Urol. 2015;193(5 Suppl):1791-5.
26. Boysen WR, Ellison JS, Kim C, Koh CJ, Noh P, Whittam B, et al. Multi-Institutional Review of Outcomes and Complications of Robot-Assisted Laparoscopic Extravesical Ureteral Reimplantation for Treatment of Primary Vesicoureteral Reflux in Children. J Urol. 2017;197:1555-61.
27. Kurtz MP, Leow JJ, Varda BK, Logvinenko T, Yu RN, Nelson CP, Chung BI, Chang SL. Robotic versus open pediatric ureteral reimplantation: Costs and complications from a nationwide sample. J Pediatr Urol. 2016;12:408.e1-408.e6.
28. Wang HH, Tejwani R, Cannon GM Jr, Gargollo PC, Wiener JS, Routh JC. Open versus minimally invasive ureteroneocystostomy: A population-level analysis. J Pediatr Urol. 2016;12:232.e1-6.
29. Garcia-Roig ML, Travers C, McCracken C, Cerwinka W, Kirsch JM, Kirsch AJ. Surgical Scar Location Preference for Pediatric Kidney and Pelvic Surgery: A Crowdsourced Survey. J Urol. 2017;197(3 Pt 2):911-9.
30. O'Donnell B, Puri P. Treatment of vesicoureteric reflux by endoscopic injection of Teflon. 1984. J Urol. 2002;167:1808-9; discussion 1810.
31. Kirsch AJ, Kaye JD, Cerwinka WH, Watson JM, Elmore JM, Lyles RH, et al. Dynamic hydrodistention of the ureteral orifice: a novel grading system with high interobserver concordance and correlation with vesicoureteral reflux grade. J Urol. 2009;182(4 Suppl):1688-92.
32. Läckgren G, Kirsch AJ. Surgery Illustrated - Surgical Atlas Endoscopic treatment of vesicoureteral reflux. BJU Int. 2010;105:1332-47.
33. Arlen AM, Scherz HC, Filimon E, Leong T, Kirsch AJ. Is routine voiding cystourethrogram necessary following double hit for primary vesicoureteral reflux? J Pediatr Urol. 2015;11:40.e1-5.
34. Kalisvaart JF, Scherz HC, Cuda S, Kaye JD, Kirsch AJ. Intermediate to long-term follow-up indicates low risk of recurrence after Double HIT endoscopic treatment for primary vesico-ureteral reflux. J Pediatr Urol. 2012;8:359-65.
35. Routh JC, Bogaert GA, Kaefer M, Manzoni G, Park JM, Retik AB, et al. Vesicoureteral reflux: current trends in diagnosis, screening, and treatment. Eur Urol. 2012;61:773-82.
36. Routh JC, Inman BA, Reinberg Y. Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: systematic review. Pediatrics. 2010;125:1010-9.
37. Brandström P, Esbjörner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children: III. Urinary tract infection pattern. J Urol. 2010;184:286-91.
38. Läckgren G, Wåhlin N, Sköldenberg E, Stenberg A. Long-term followup of children treated with dextranomer/hyaluronic acid copolymer for vesicoureteral reflux. J Urol. 2001;166:1887-92.
39. Friedmacher F, Colhoun E, Puri P. Endoscopic Injection of Dextranomer/Hyaluronic Acid as First Line Treatment in 851 Consecutive Children with High Grade Vesicoureteral Reflux: Efficacy and Long-Term Results. J Urol. 2018;200:650-5.
40. Lightfoot M, Bilgutay AN, Tollin N, Eisenberg S, Weister J, Bryan L, Smith E, et al. Long-Term Clinical Outcomes and Parental Satisfaction After Dextranomer/Hyaluronic Acide (Hx/HA) Injection for Primary Vesicoureteral Reflux. Front Pediatr 2019;7:392. available at. <https://www.frontiersin.org/articles/10.3389/fped.2019.00392/full>.

41. Chertin B, Arafeh WA, Zeldin A, Ostrovsky IA, Kocherov S. Endoscopic correction of VUR using vantris as a new non-biodegradable tissue augmenting substance: three years of prospective follow-up. Urology. 2013;82:201-4.
42. Ormaechea M, Ruiz E, Denes E, Gimenez F, Dénes FT, Moldes J, et al. New tissue bulking agent (polyacrylate polyalcohol) for treating vesicoureteral reflux: preliminary results in children. J Urol. 2010;183:714-7.
43. Kocherov S, Ulman I, Nikolaev S, Corbetta JP, Rudin Y, Slavkovic A, et al. Multicenter survey of endoscopic treatment of vesicoureteral reflux using polyacrylate-polyalcohol bulking copolymer (Vantris). Urology. 2014;84:689-93.
44. Alizadeh F, Omidi I, Haghdani S, Hatef Khorrami M, Izadpanahi MH, Mohammadi Sichani M. A comparison between dextranomer/ hyaluronic acid and polyacrylate polyalcohol copolymer as bulking agents for treating primary vesicoureteral reflux. Urol J. 2019;16:174-9.
45. Blumenthal-Barby J, Opel DJ, Dickert NW, Kramer DB, Tucker Edmonds B, Ladin K, et al. Potential Unintended Consequences Of Recent Shared Decision Making Policy Initiatives. Health Aff (Millwood). 2019;38:1876-81.
46. Garcia-Roig M, Travers C, McCracken CE, Kirsch AJ. National Trends in the Management of Primary Vesicoureteral Reflux in Children. J Urol. 2018;199:287-93.

Correspondence address:
Andrew J. Kirsch, MD
Emory University School of Medicine
Children's Healthcare of Atlanta
5730 Glenridge Drive, Suite 200
Atlanta, GA 30328, USA
Fax: +1 404 252-1268
E-mail: akirschmd@gmail.com

REVIEW ARTICLE

Vol. 46 (3): 322-327, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.99.03

Robotics in Pediatric Urology

Molly E. Fuchs [1], Daniel G. DaJusta [1]

[1] *Nationwide Children's Hospital, Columbus, OH, USA*

ABSTRACT

Robotic surgery has been slow to be fully accepted in the world of pediatric urology largely because of its initial application directed towards adult use and because of the inherent high cost associated with it. However, as previously shown, it has now become the gold standard for adolescent pyeloplasty in The United States. As the adoption of robotic surgery in children has become more widespread, its use has been applied to a broader spectrum of procedures with similar success rates to standard laparoscopy. These procedures include nephrectomy, heminephrectomy, ureteral reimplantation, and ureteroureterostomy. However, it has also shown feasibility and comparable success when compared to open surgery in procedures that were previously deemed too complex to be done by standard laparoscopy. For example, bladder neck reconstruction with Mitrofanoff and Malone procedure as well as bladder augmentation. This review objective is to provide an overview of robotic surgery in pediatric urology, with a focus on the more common cases such as pyeloplasty and reimplantation as well as more complex bladder reconstruction procedures.

ARTICLE INFO

Daniel DaJusta
http://orcid.org/0000-0002-0454-0704

Keywords:
Pediatrics; Robotics; Laparoscopy

Int Braz J Urol. 2020; 46: 322-7

Submitted for publication:
December 15, 2019

Accepted after revision:
December 20, 2019

Published as Ahead of Print:
January 06, 2020

INTRODUCTION

The benefits of laparoscopic surgery over open surgery are undeniable. The decrease in post-operatory pain narcotic use, blood loss and expedited recovery have helped propel the popularity of laparoscopic surgery. The learning curve has continued to be the limiting factor, particularly for more complex procedures involving intracorporeal suturing and extensive reconstruction. The popularity of laparoscopic extirpative procedures such as cholecystectomy and nephrectomy has grown to the point that they are now more common than their open counterparts. Yet, for more complex types of surgery, this trend has not seemed to hold true. Few centers were attempting laparoscopy for complex procedures such as prostatectomy and pyeloplasty and it did not seem that the laparoscopic approach would be favored over the open approach. This was largely related to the complexity of these cases and the steep learning curve associated with such procedures. It appeared that laparoscopy would not be widely adopted for complex cases until the robotic approach was introduced.

There are several primary benefits of robotic surgery over standard laparoscopic. First, 3-dimensional vision with 10 times magnification. This allows for depth perception that is lacking in

standard laparoscopy. Second, the robotic EndoWrist instruments that allow for 7 degrees of movement freedom that far outperforms the standard laparoscopic instruments that provide limited maneuverability. Finally, in stark contrast to standard laparoscopy, the movements of the arms under the view of the camera are not inverted. As a result, the robotic platform provides more intuitive movements and proficiency is more readily acquired. The only significant limitations of robotic surgery are cost and the lack of tactile feedback, although robotic surgeons eventually overcome the lack of tactile feedback using visual cues provided by the improved optics.

As a result of these advantages, the introduction of robotics as a tool for laparoscopic surgery has allowed for many previously complex laparoscopic cases to become mainstream. Laparoscopic prostatectomy is a prime example of the robotic surgery allowing for the adoption of a minimally invasive technique. Prior to the introduction of the robotics, laparoscopic prostatectomy had been performed by a select few surgeons and because of the difficulties mastering the procedure with this technique, it failed to become adopted. In contrast, since the introduction of the robotic assisted prostatectomy, which has a more readily adoptable skill set and less steep learning curve, this technique has quickly become the gold standard in a very short period of time (1, 2). There are many similar examples of complex reconstructive surgeries that are now becoming feasible and more commonly performed due to the availability of the robotic platform.

In pediatrics, robotic pyeloplasty is the primary example of how the introduction of robotics has helped a laparoscopic technique transition from second-line therapy to the standard of care. Laparoscopic pyeloplasty was described as early as 1993 and has shown to have similar success rates as open pyeloplasty but with the added benefits of minimally invasive laparoscopic as previously discussed (3, 4). However, prior to the introduction of robotics had never been able to overtake the open surgery as the procedure of choice. A recent longitudinal evaluation of practice patterns across the US showed that in 2003, 10 years after being first described, laparoscopic pyeloplasty only accounted for <20 % of the pyeloplasties performed in patients aged 13-18 years. In contrast, ten years after robotic pyeloplasty was introduced in 2015, >80% of pyeloplasties were being performed robotically in this same age group in the United States (5). This study reinforces the sentiment that robotic assisted technique is more readily adoptable and has a more favorable learning curve compared to standard laparoscopy. Therefore, the popularity of the robotic platform continues to grow in the pediatrics. Complex reconstructive cases such as bladder neck reconstruction in neurogenic bladder, have now been performed using the robotic surgery. This technique has yet to be shown superior to its open counterpart, though this may be due to the limited number of cases performed to date.

ROBOTIC PYELOPLASTY

As previously mentioned, the popularity of robotic pyeloplasty rose quickly and is now the gold standard for adolescent patients across the United States. In patients between 1-12 years of age, it is becoming the procedure of choice and in 2015, >40% of these patients were done robotically (5). In infants (<1 year of age), the use of robotic technique remains controversial, despite multiple reports showing the feasibility and excellent outcomes comparable to open surgery (6). The primary factors that contribute to surgeons' reluctance to adopt this technique in infants is likely the decreased intraabdominal space and the 8 mm port size of the current robotic platform. Indeed, the authors would recommend prior to attempting robotic infant pyeloplasty that the surgeon does become well familiar with performing it in bigger size patients.

One major benefit of using robotic surgery is improved ergonomics which facilitates intracorporeal suture and as a result operative times have improved when compared to standard laparoscopy. Most published series have shown a decrease in operative time with the robotic approach as well as fewer complications (7). Furthermore, the learning curve with the robot has been shown to be far shorter than with laparoscopy, thus new surge-

ons are able to reach the curve plateau faster (8). As a result, the number of patients exposed to the beginning of the learning curve is smaller which ultimately translates to better outcomes for patients.

Furthermore, the improved maneuverability afforded by the robot has allowed for different port positions with potential cosmetic and functional benefits. The HIdES port placement technique works extremely well for pyeloplasty irrespective of the patients' anatomy. While this type of port position does take some time to get used to, it does provide better cosmetic outcomes when compared to open surgery and standard robotic port position (9). When utilizing the HIdES technique, the surgeon must be extremely careful while placing the suprapubic camera port in a smaller patient in order to avoid a bladder injury.

The use of an internal stent has been long mention as a drawback associated with the robotic as well as laparoscopic techniques. Given that most open cases are done with an external nephroureteral stent that can be removed a week later in the office. Leaving a stent will lead to the need for an additional procedure to remove it. While this is less than ideal, several possible solutions exist. First, the stent can be placed in a retrograde fashion at the beginning of the operation and left attached to a string for later retrieval in the office. Second, given the improved optics and watertight anastomosis from running robotic suturing, a stent free pyeloplasty can be done. This later technique has been described with promising results (10). Thus, given the reported success of robotic stentless pyeloplasty, it does not seem that the stent has much impact on the overall outcome of the procedure and its use can be left to surgeons' preference.

Due to the benefits afforded by the smaller trocar incisions in laparoscopy and robotics, hospital stay continues to decrease. In most current robotic series, the hospital stay has decreased to <24 hours. With the development of Early Recovery After Surgery (ERAS) protocols, this time frame will continue to improve. To this date, only a few have reported on same day discharge after robotic pyeloplasty, but this may come to be the norm rather than the exception in the future (11).

ROBOTIC REIMPLANTATION

Robotic ureteral reimplantation is currently a controversial topic in pediatric urology. The most common robotic technique utilized is a Lich-Gregoir extravesical approach. Multiple publications have shown that the Lich-Gregoir reimplant has similar success rates as intravesical reimplantation techniques such as the Cohen reimplant (12). Therefore, one would expect similar success rates when this technique is applied robotically. However, while the initial single-center series showed promise, a multicenter study cast serious doubt on the initial results with a success rate well below that of the open procedure (13). Furthermore, the complication rate with the robotic technique was higher when compared to open series and more than 10% of the patient required reoperation for persistent reflux or a complication. These results have caused many to reconsider the use of the robotic technique for ureteral reimplantation.

Nevertheless, two recent series, also combined results from multiple institutions to achieve a greater number of patients, showed improve success rates and a complication rate similar to open procedures (14, 15). These studies pointed out a steeper learning curve associated with this procedure as the possible cause of the initial concerning results. Another possible explanation could be related to the decreasing number of reimplantation surgeries due to the use of a more conservative approach to lower grade reflux. The above mention reasons, coupled with the fact that surgery is now only being done for a higher grade of VUR could serve as possible explanations for the initial disappointing results.

One of the main drawbacks associated with the extravesical reimplantation technique is the possibility of temporary postoperative urinary retention (14). This seems to occur at higher rates when performing a bilateral procedure as well as in patients with a prior history of voiding dysfunction. Yet, recent series have come to challenge this notion, showing other factors may play a role in the development of retention following surgery (16). Nevertheless, the surgeon needs to be aware of this complication and discuss it with the family

as the patient may require intermittent catheterization usually for a short period after surgery.

While less commonly performed, laparoscopic vesicoscopic cross trigonal reimplantation has shown promise and comparable success rates (17). By insufflating and placing ports directly in the bladder, this technique avoids intraperitoneal port placement. Additionally, as this is a cross trigonal intravesical reimplantation, it carries little to no risk of urinary retention. It is a very challenging technique to master and the number of published series is limited. While it was thought that the robotic technique could make this technique more accessible, this has not been the case so far. To this date, outside of sparse case reports, large series of robotic vesicoscopic cross trigonal reimplantation has not been described in the literature (18).

While this controversy will persist, the authors believe that for an older patient with unilateral reflux robotic assisted laparoscopic extravesical reimplantation is a good surgical option. In this patient population where the bladder is usually deep in the pelvis, which can make open surgery difficult, the robotic procedure may have an edge. This may be supported by the more recent series showing similar results for the robotic technique versus open and with the prospect of faster recovery given the smaller incisions.

ROBOTIC COMPLEX BLADDER RECONSTRUCTION

While rarely done in the past using the standard laparoscopic technique, minimally invasive complex bladder reconstruction has become a viable surgical option in pediatric patients since the introduction of the robot. The main indication for complex reconstructive surgery in pediatrics remains tied to the goal of achieving continence in patients with neurogenic bladder. This population's incontinence is usually secondary to bladder outlet incompetence, bladder overactivity, or a combination of the two problems. Bladder outlet incontinence will require a reconstructive outlet procedure most commonly coupled with a catheterizable channel while intractable bladder overactivity usually requires augmentation. Procedures such as Mitrofanoff, bladder neck reconstruction, and augmentation, are now able to be completed entirely laparoscopically with the aid of the robot and their feasibility has been clearly established. Additionally, outcomes for these surgeries performed with the robot have been comparable to their open technique counterparts. However, the overall number of patients that require these procedures is low when compared to other more common procedures such as pyeloplasty. This has hindered the ability to demonstrate the well-known benefits of robotic surgery in these procedures.

There are two strong recommendations by the authors to any surgeon undertaking robotic bladder reconstruction. First, the preoperative mechanical bowel preparation is critical. The bowel preparation's main purpose is to help increase the already limited intraabdominal space. Given that a lot of these patients have concomitant constipation related to neurogenic bowel, this can create a significant issue with intraabdominal working space if not address pre-operative. Second, these authors recommend injecting intra-detrusor Botox concomitantly with the bladder reconstruction. The bladder Botox injection has been shown to help with the post-operative bladder spasms as well as pain control (19).

Robotic-assisted technique for catheterizable channels such as appendicovesicostomy has been shown to be not just a feasible option but also has a reasonable amount of benefit. Thus far, of the bladder reconstruction procedures, robotic Mitrofanoff has the largest number of cases in the literature. A multicenter study that included 88 patients undergoing robotic Mitrofanoff with a follow up of 29.5 months, showed that the technique is reproducible across centers (20). It also demonstrated comparable complication rates and functional outcomes to previously published series of open Mitrofanoff.

Robotic bladder outlet procedure was first described by Gargollo, demonstrating the concept of feasibility (21). After the initial description, a comparison series between open and robotic cases showed similar continence outcomes and complications. The operative time was significantly lon-

ger in the robotic group. However, hospital length of stay was similar, thus there was no specific benefit to the robotic technique (22).

Robotic bladder augmentation feasibility has been well established in the literature. Additionally, functional outcomes were compared on a recent series to the open technique showing a similar increase in bladder capacity, narcotic use and complication rates between groups. The length of surgery was longer for robotic (627 vs. 265 minutes) while the length of stay was one day shorter for the robotic cohort, though this was not significant (23). Again, during the initial experience with these procedures, the usual benefits of the robotic technique have not been as evident as one would have expected.

These bladder reconstructions are complex procedures and should be performed by experienced robotic surgeons. The initial learning curve is steep, and these procedures typically take many hours longer to perform compared to their open counterparts. However, as surgeons experience grows, operative times do decrease and one cannot deny the many benefits afforded to the surgeon with the robotic technique. As the experience with these cases increases, the known benefits of laparoscopic surgery such as decreased hospital stay and narcotic use should also become evident for complex bladder reconstruction procedures.

CONCLUSIONS

While this once seemed far in the future, robotic surgery in pediatric urology has become part of the surgeon's reality. The many benefits afforded by the robot have made laparoscopic surgery techniques accessible to surgeons. Novice laparoscopic surgeons can benefit from the shorter learning curve while skilled surgeons should be able to push the limits of what can be done laparoscopically with the application of the robotic technique. This will hopefully continue to drive towards the goal of better outcomes for the patients. There are clear benefits to using robotic surgery in pediatric urology, particularly in cases such as pyeloplasty. Its application to complex bladder reconstruction is still limited to a select few but is being applied more widely each year and this growth is limited only by the low volume of such complex procedures.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sammon JD, Karakiewicz PI, Sun M, Sukumar S, Ravi P, Ghani KR, et al. Robot-assisted versus open radical prostatectomy: the differential effect of regionalization, procedure volume and operative approach. J Urol. 2013;189:1289-94.
2. Basiri A, de la Rosette JJ, Tabatabaei S, Woo HH, Laguna MP, Shemshaki H. Comparison of retropubic, laparoscopic and robotic radical prostatectomy: who is the winner? World J Urol. 2018;36:609-21.
3. Kavoussi LR, Peters CA. Laparoscopic pyeloplasty. J Urol. 1993;150:1891-4.
4. Mei H, Pu J, Yang C, Zhang H, Zheng L, Tong Q. Laparoscopic versus open pyeloplasty for ureteropelvic junction obstruction in children: a systematic review and meta-analysis. J Endourol. 2011;25:727-36.
5. Varda BK, Wang Y, Chung BI, Lee RS, Kurtz MP, Nelson CP, et al. Has the robot caught up? National trends in utilization, perioperative outcomes, and cost for open, laparoscopic, and robotic pediatric pyeloplasty in the United States from 2003 to 2015. J Pediatr Urol. 2018;14:336.e1-336.e8.
6. Bansal D, Cost NG, DeFoor WR Jr, Reddy PP, Minevich EA, Vanderbrink BA, Alam S, Sheldon CA, Noh PH. Infant robotic pyeloplasty: comparison with an open cohort. J Pediatr Urol. 2014;10:380-5.
7. Silay MS, Spinoit AF, Undre S, Fiala V, Tandogdu Z, Garmanova T, et al. Global minimally invasive pyeloplasty study in children: Results from the Pediatric Urology Expert Group of the European Association of Urology Young Academic Urologists working party. J Pediatr Urol. 2016;12:229.e1-7.
8. Tasian GE, Wiebe DJ, Casale P. Learning curve of robotic assisted pyeloplasty for pediatric urology fellows. J Urol. 2013;190(4 Suppl):1622-6.
9. Gargollo PC. Hidden incision endoscopic surgery: description of technique, parental satisfaction and applications. J Urol. 2011;185:1425-31.

10. Silva MV, Levy AC, Finkelstein JB, Van Batavia JP, Casale P. Is peri-operative urethral catheter drainage enough? The case for stentless pediatric robotic pyeloplasty. J Pediatr Urol. 2015;11:175.e1-5.
11. Finkelstein JB, Van Batavia JP, Casale P. Is outpatient robotic pyeloplasty feasible? J Robot Surg. 2016;10:233-7.
12. Silay MS, Turan T, Kayalı Y, Başıbüyük İ, Gunaydin B, Caskurlu T, et al. Comparison of intravesical (Cohen) and extravesical (Lich-Gregoir) ureteroneocystostomy in the treatment of unilateral primary vesicoureteric reflux in children. J Pediatr Urol. 2018;14:65.e1-65.e4.
13. Grimsby GM, Dwyer ME, Jacobs MA, Ost MC, Schneck FX, Cannon GM, et al. Multi-institutional review of outcomes of robot-assisted laparoscopic extravesical ureteral reimplantation. J Urol. 2015 May;193(5 Suppl):1791-5.
14. Boysen WR, Ellison JS, Kim C, Koh CJ, Noh P, Whittam B, et al. Multi-Institutional Review of Outcomes and Complications of Robot-Assisted Laparoscopic Extravesical Ureteral Reimplantation for Treatment of Primary Vesicoureteral Reflux in Children. J Urol. 2017;197:1555-61.
15. Boysen WR, Akhavan A, Ko J, Ellison JS, Lendvay TS, Huang J, et al. Prospective multicenter study on robot-assisted laparoscopic extravesical ureteral reimplantation (RALUR-EV): Outcomes and complications. J Pediatr Urol. 2018;14:262.e1-262.e6.
16. Kawal T, Srinivasan AK, Chang J, Long C, Chu D, Shukla AR. Robotic-assisted laparoscopic ureteral re-implant (RALUR): Can post-operative urinary retention be predicted? J Pediatr Urol. 2018;14:323.e1-323.e5.
17. Jayanthi VR. Vesicoscopic cross-trigonal ureteral reimplantation: High success rate for elimination of primary reflux. J Pediatr Urol. 2018;14:324.e1-324.e5.
18. Peters CA, Woo R. Intravesical robotically assisted bilateral ureteral reimplantation. J Endourol. 2005;19:618-21; discussion 621-2.
19. Fuchs ME, Beecroft N, McLeod DJ, Dajusta DG, Ching CB. Intraoperative Onabotulinumtoxin-A Reduces Postoperative Narcotic and Anticholinergic Requirements After Continent Bladder Reconstruction. Urology. 2018;118:183-8.
20. Gundeti MS, Petravick ME, Pariser JJ, Pearce SM, Anderson BB, Grimsby GM, et al. A multi-institutional study of perioperative and functional outcomes for pediatric robotic-assisted laparoscopic Mitrofanoff appendicovesicostomy. J Pediatr Urol. 2016;12:386.e1-386.e5.
21. Bagrodia A, Gargollo P. Robot-assisted bladder neck reconstruction, bladder neck sling, and appendicovesicostomy in children: description of technique and initial results. J Endourol. 2011;25:1299-305.
22. Grimsby GM, Jacobs MA, Menon V, Schlomer BJ, Gargollo PC. Perioperative and Short-Term Outcomes of Robotic vs Open Bladder Neck Procedures for Neurogenic Incontinence. J Urol. 2016;195(4 Pt 1):1088-92.
23. Cohen AJ, Brodie K, Murthy P, Wilcox DT, Gundeti MS. Comparative Outcomes and Perioperative Complications of Robotic Vs Open Cystoplasty and Complex Reconstructions. Urology. 2016;97:172-8.

Correspondence address:
Daniel G. DaJusta, MD
Nationwide Children's Hospital
700 Children's Dr
Columbus, OH, 43205, USA
E-mail: daniel.dajusta@nationwidechildrens.org

REVIEW ARTICLE

Vol. 46 (3): 328-340, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0423

Exploration of IMDC model in patients with metastatic renal cell carcinoma using targeted agents: a meta-analysis

Guiya Jiang [1, 2], Shuqiu Chen [1,2], Ming Chen [1,2]

[1] *School of Medicine, Southeast University, China;* [2] *Department of Urology, Southeast University, Zhongda Hospital, NanJing, 210009, China*

ABSTRACT

Purpose: To explore the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model application for predicting outcome of patients with metastatic renal cell carcinoma using targeted agents.
Materials and Methods: We performed a literature review of 989 articles. The selecting process used preferred reporting items for systematic reviews and meta-analyses (PRISMA). All included studies were assessed by Newcastle-Ottawa scale. Results of individual studies were pooled using Stata 14.0 software.
Results: A total of 17 articles were included. Most articles provided univariate and multivariate analysis of IMDC model prognosis. Combined HRs were 1.58 (95% CI 1.34-1.82) and 3.74 (95% CI 2.67-4.81) for univariate PFS of intermediate to favorable and poor to favorable respectively. In the category of multivariate PFS, combined HRs were 1.27 (95% CI 0.99-1.56) and 2.29 (95% CI 1.65-2.93) with intermediate to favorable and poor to favorable respectively. Regarding univariate OS, combined HRs were 1.93 (95% CI 1.62-2.24) and 6.25 (95% CI 4.18-8.31) with intermediate to favorable and poor to favorable respectively. With multivariate OS, combined HRs were 1.32 (95%CI 1.04-1.59) and 2.35 (95%CI 1.69-3.01) with intermediate to favorable and poor to favorable respectively.
Conclusion: In summary, analysis of currently available clinical evidence indicated that IMDC model could be applied to classify patients with metastatic renal cell carcinoma using targeted agents. However, different types of targeted agents and various areas could affect the accuracy of the model. There was also a difference in predicting patients' PFS and OS.

ARTICLE INFO

Shuqiu Chen
http://orcid.org/0000-0003-4117-1917

Keywords:
Carcinoma, Renal Cell; Meta-Analysis [Publication Type]; Prognosis

Int Braz J Urol. 2020; 46: 328-40

Submitted for publication:
June 27, 2019

Accepted after revision:
October 22, 2019

Published as Ahead of Print:
December 30, 2019

INTRODUCTION

Renal cell carcinoma (RCC) represents approximately 3% of all cancers, with the highest incidence occurring in western countries. Generally, during the last two decades, there has been an annual increase of 2% in incidence both worldwide and in Europe, leading to approximately 99, 200 new RCC cases and 39.100 kidney cancer-related deaths within the European Union in 2018 (1). According to the 2019 tumor statistics, there were 44.120 new kidney cancer men and 29.700 women in the United States, with the incidence rates being third and eighth respectively (2). Although most RCC cases are diagnosed at an early stage, approximately 20% of patients undergoing curati-

ve nephrectomy will subsequently develop metastasis during the follow-up period (3). Many new therapeutic drugs have emerged, such as immune checkpoint drugs based on PD-1/PD-L1 or CTLA4 as representative drugs, targeted agents are still the mainstream drugs for the treatment of metastatic renal cell carcinoma. Because of the poor prognosis of metastatic renal cell carcinoma, it is important to choose appropriate prognostic factors for communication with patients and their families, to determine treatment options, and to group people in clinical trials. The most widely used prognostic models for the prognosis of metastatic renal cancer is International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model (4). IMDC model was based on prognostic data from populations treated with various targeted drugs (5). Although the applicability of the model has been verified by some articles like Kwon's article (6), there are also articles like Peltola's (7) article that provide different conclusions. Therefore, we conducted this study to explore the IMDC model application for predicting outcome in patients with metastatic renal cell carcinoma using targeted agents.

MATERIALS AND METHODS

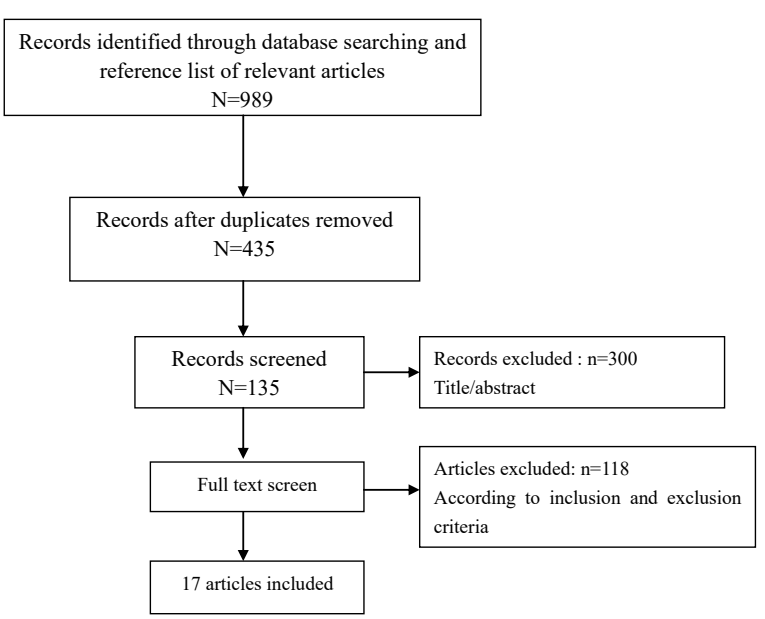
Search strategy

We performed a literature review of articles published before June 31, 2019 using the PubMed, Web of Sciences and Embase Databases. The main search terms used were "metastatic renal carcinoma", "prognosis", "TKI", "mTORi", "sunitinib", "sorafenib", "pazopanib", "axitinib", "bevacizumab", "everolimus", " temsirolimus" et al. and their combinations. Additional references were identified from the reference list of each article. Two reviewers carried out this process independently. The selecting process using preferred reporting items for systematic reviews and meta-analyses (PRISMA) (8) statement was exhibited in Figure-1 following the inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) patients were confirmed with metastatic renal carcinoma pathologically, (2) used targeted agents, (3) provided survival outcome based on IMDC model such as progression-free survival (PFS) or overall survival (OS) with hazard ratio (HR) and 95% confidence intervals (95% CI).

Figure 1 - Selective process using preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.



Exclusion criteria: (1) cohort of patients including other therapy like cytokine or immune checkpoint drugs, (2) articles providing data from the same population, (3) not in English.

Data synthesis and analysis

All included studies were assessed by Newcastle-Ottawa scale which provided a score from a possible total of nine scores. Key quality areas assessed included: (1) selection of study groups, (2) comparability of the groups, and (3) assessment of the outcome. High scores indicated high quality, a study with a score ≥6 was regarded as high quality, while a score <6 was regarded as moderate or low quality (9). Results of individual studies were pooled using Stata 14.0 software (Stat Corp, College Station, TX, USA). Meta-analytical method was inverse variance method. We used the I^2 statistic test to assess the heterogeneity between studies. I^2 ranges are from 0% to 100% (a value of 0% represents no heterogeneity, 0% <I^2 <25% represents mild, 25% ≤I^2 <50% represents moderate, 75% ≤I^2 represents great heterogeneity). When I^2 <50% or $P_{heterogeneity}$ >0.1, no obvious heterogeneity existed among the studies. To achieve a relatively conservative conclusion, the random-effects (RE) model was applied (10, 11). Publication bias was assessed using a funnel plot and Egger's test. Sensitivity analysis was used to estimate the robustness of pooled results. P value <0.05 was considered to be statistically significant difference in studies.

RESULTS

Characteristics of included studies

According to the search strategy, 989 articles were retrieved from the electronic databases. By excluding duplicate reports and screening the abstracts, 135 articles were read by full text. The remaining articles were further excluded upon full-text review for several reasons, such as a lack of sufficient data to estimate HRs or duplicate publication in repeated cohorts. Finally, 17 articles were included for meta-analysis and the summary characteristics of articles were obtained (Table-1). Some articles provided different data from similar cohort of patients. Most articles provided univariate and multivariate analysis of HRs involving different factors for PFS and OS and we exhibited pooled results respectively.

Univariate PFS

There were 8 articles (12-19) including 1618 patients in this category, and Kawai's article (17) provided HR of poor to favorable only. Among these patients, 1454 were clear cell RCC and 163 were non clear cell RCC, favorable, intermediate and poor risk group has 401, 821, 336 patients respectively. Sunitinib was the most commonly used agent.

Intermediate to favorable

The combined HR was 1.58 (95% CI 1.34-1.82) and the forest plot is shown in Figure-2. According to funnel plot and egger's test (p=0.308), there was no publication bias. And sensitivity analysis showed the result was robust. Subgroup analysis showed the model was applicable in both Asia and other areas (Supplementary Figure-1). Whether the cohort of patients all took sunitinib alone or part of patients took sorafenib or pazopanib or temsirolimus, the model could effectively distinguish between favorable and intermediate--risk group (Supplementary Figure-2).

Poor to favorable

The combined HR was 3.74 (95% CI 2.67-4.81) and the forest plot is shown in Figure-2. According to funnel plot and Egger's test (p=0.911), there was no publication bias. And sensitivity analysis showed the result was robust. Subgroup analysis showed the model was reliable in both Asia and other areas (Supplementary Figure-1). Whether the cohort of patients all took sunitinib alone or part of patients took sorafenib or pazopanib or temsirolimus, the model could separate patients between favorable and poor-risk group (Supplementary Figure-2).

Multivariate PFS

There were 7 articles (7, 12, 16, 17, 19-21) I ncluding 1087 patients in the category, and Kawai's article (17) still provided HR of poor to favorable only. Among these patients, 918 were clear cell RCC and 145 were non clear cell RCC, favorable, intermediate and poor risk groups have

Table 1- The summary characteristics of 17 included articles.

Author	Year	Country	Drug	Lines	Patient	Period	Follow-up (months)
Keizman	2014	Israel/US	Suni	combined	278	2004/2/1-2013/3/31	55
Yao	2018	China	suni or sora	NA	231	2007-2017	NA
Peltola	2017	Finland	suni	first line	137	2006/10/18-2012/5/31	NA
Kawai	2015	Japan	suni	first line	46	2008/11/1-2013/7/1	21.2
Giorgi	2014	Italy	suni	first line	181	2006/2/1-2011/9/1	30.4
Auclin	2017	France	evero	no first line	124	2007/2/1-2014/11/1	NA
Cai	2017	China	suni or sora	first line	143	2006/3/1-2015/7/1	22
Benoit	2013	Belgium/France	suni	first line	200	2005/1/1-2012/10/1	67
Bamias	2014	Greece/France/Belgium	suni	first line	186	2005/10/1-2012/1/1	34.07
Xia	2017	China	suni or sora	first line	110	2005/3/1-2014/6/1	NA
Wang	2016	China	suni or sora	first line	111	2005/3/1-2014/6/1	19.7
Miyake	2016	Japan	suni	first line	50	2008/5/1-2013/7/1	20
Lin	2019	China	suni or sora	first line	108	2005/3/1-2014/6/1	23.35
Kwon	2013	Korea	suni or sora	first or second	106	2007/4/1-2012/7/1	NA
Lolli	2016	Italy	suni	first line	335	NA	49
You	2016	Korea	suni, sora, pazo, or temsi	first line	325	2006/11/1-2013/6/1	NA
Kim	2018	Korea	suni or pazo	first line	554	2012/1/1-2016/11/1	16.4

Author	ccRCC	nccRCC	Favorable	Intermediate	Poor	NOS	Outcome	Survival time(months)
Keizman	211	67	60	163	55	7	PFS/OS	9/22
Yao	199	32	38	153	40	7	OS	17.5
Peltola	105	15	29	74	31	7	PFS/OS	8.6/24.4
Kawai	46	0	2	26	18	6	PFS/OS	9.6/18.1
Giorgi	165	16	44	103	33	7	PFS/OS	11/25.5
Auclin	109	15	40	62	22	7	OS	12.9
Cai	136	7	62	59	22	6	PFS/OS	11/27
Benoit	200	0	13	55	33	7	PFS/OS	12/20
Bamias	173	12	33	83	35	6	OS	20.96
Xia	88	22	22	60	68	7	PFS/OS	9.8/23.5
Wang	89	22	23	60	28	6	PFS/OS	NA
Miyake	40	4	10	29	11	6	PFS/OS	8.9/23.5
Lin	87	21	23	58	27	7	PFS/OS	NA
Kwon	85	21	18	54	16	7	PFS/OS	12/17.8
Lolli	315	20	117	176	42	6	PFS/OS	14.2/32.7
You	293	31	81	179	65	7	PFS/OS	16.2/26.1
Kim	NA	NA	114	345	90	6	OS	36.2/40.5

Suni = sunitinib; **Sora =** sorafenib; **pazo =** pazopanib; **evero =** everolimus; **temsi =** temsirolimus

267, 588, and 229 patients respectively. Sunitinib was the most commonly used agent.

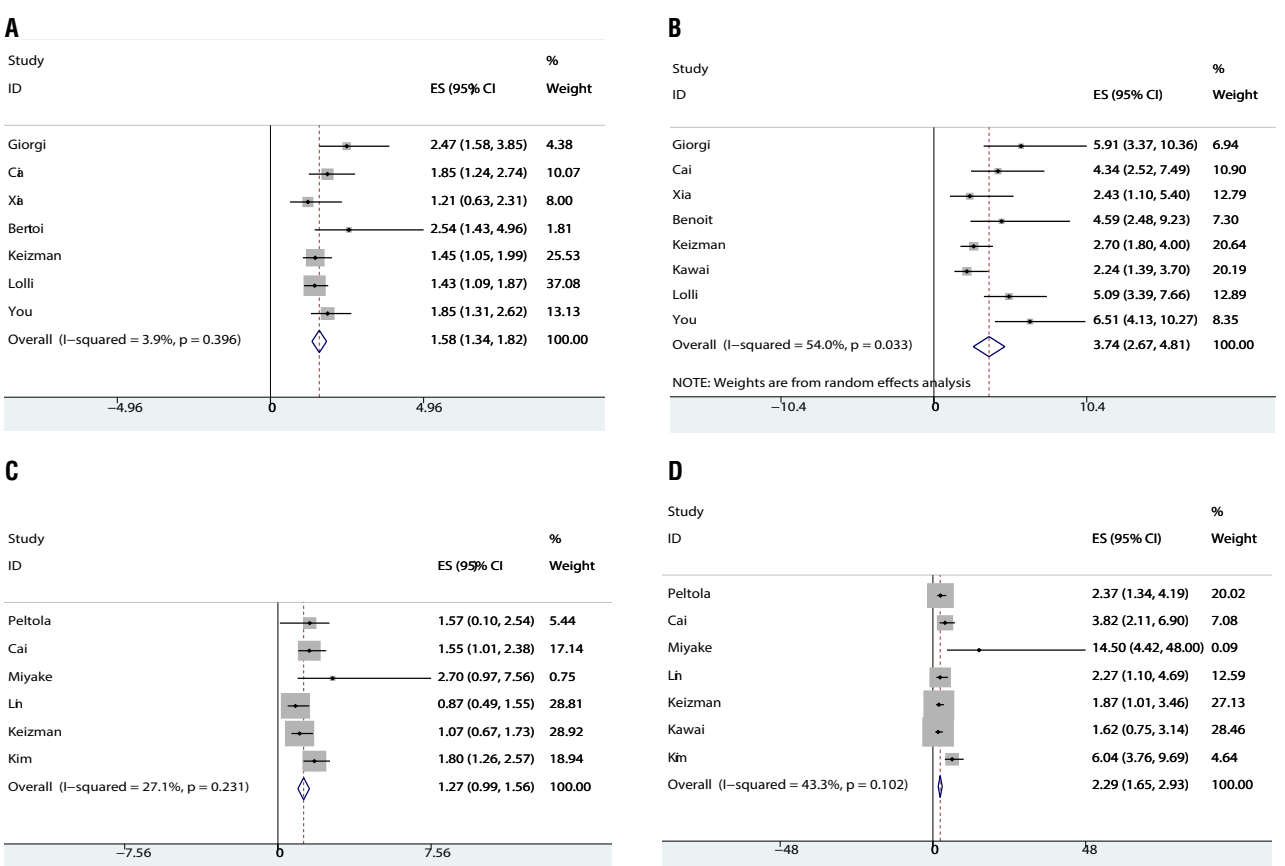
Intermediate to favorable

The combined HR was 1.27 (95% CI 0.99-1.56) and the forest plot is shown in Figure-2. According to funnel plot and Egger's test (p=0.983), no publication bias was detected. And sensitivity analysis showed the result was not robust. When Lin and Keizman's article was omitted, the result changed to 1.43 (95% CI 1.09-1.77) and 1.35 (95% CI 1.01-1.69) respectively. Interestingly, only in Keizman's article the targeted agents were not used as first line therapy. Subgroup analysis showed the model was not applicable in both Asia and other areas (Supplementary Figure-1). Whether the cohort of patients all took sunitinib alone or part of patients took sorafenib or pazopanib or temsirolimus, the model was not efficient between favorable and intermediate-risk group (Supplementary Figure-2).

Poor to favorable

The combined HR was 2.29 (95% CI 1.65-2.93) and the forest plot is shown in Figure-2. According to funnel plot and Egger's test (p=0.962), no publication bias was detected. And sensitivity analysis showed the result was robust. Subgroup analysis showed the model was applicable in both Asia and other areas (Supplementary Figure-1). Whether the cohort of patients all took sunitinib alone or part of patients took sorafenib or pazopanib, the model was efficient to classify favorable and poor-risk group (Supplementary Figure-2).

Figure 2 - Combined HRs of IMDC model from PFS.



a) forest plot of univariate analysis of intermediate to favorable risk group; **b)** forest plot of univariate analysis of poor to favorable risk group; **c)** forest plot of multivariate analysis of intermediate to favorable risk group; **d)** forest plot of multivariate analysis of poor to favorable risk group.

Univariate OS

In all 10 articles (6, 12-14, 16, 18, 18, 22-24) including 2419 patients in the category, among these patients, 1667 were clear cell RCC and 196 were non clear cell RCC. It was unfortunate that Kim's article did not provide specific number of patients with different pathological types. Favorable, intermediate and poor risk group had 565, 1227, and 419 patients respectively.

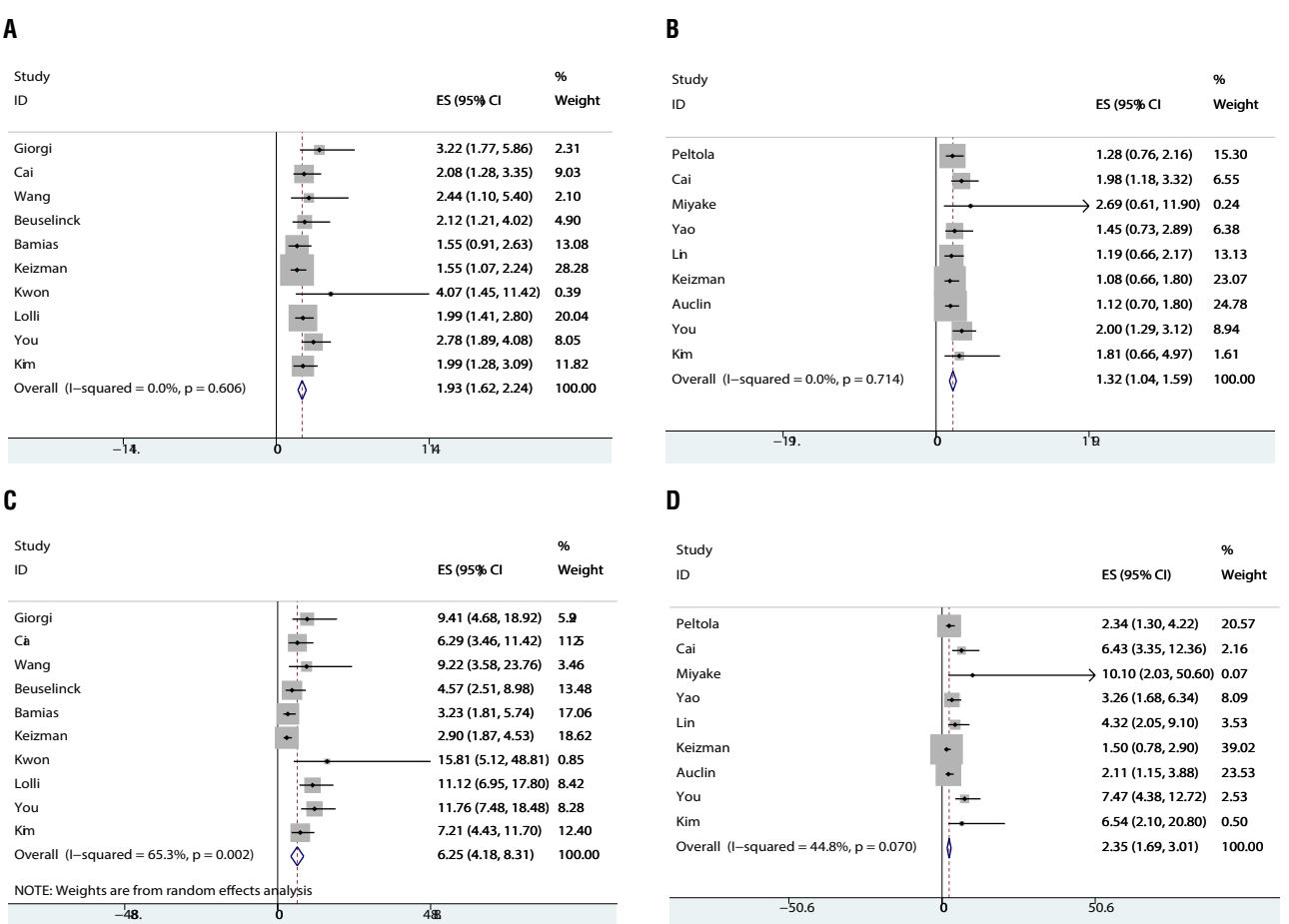
Intermediate to favorable

The combined HR was 1.93 (95% CI 1.62-2.24) and the forest plot is shown in Figure-3. According to funnel plot and Egger's test (p=0.194), no publication bias was detected. Sensitivity analysis showed the result was robust. Subgroup analysis showed the model was applicable in both Asia and other areas (Supplementary Figure-3). Whether the cohort of patients all took sunitinib alone or part of patients took sorafenib or pazopanib or temsirolimus, the model was efficient to classify favorable and intermediate-risk group (Supplementary Figure-4).

Poor to favorable

The combined HR was 6.25 (95% CI 4.18-8.31) and the forest plot is shown in Figure-3. According to funnel plot and Egger's test (p=0.596), no publication bias was detected. Sensitivity analysis showed the result was robust. Subgroup analysis showed the model was applicable in both Asia and other areas (Supplementary Figure-3). Whether the cohort of patients all took sunitinib alone or part of

Figure 3 - Combined HRs of IMDC model from OS.



a) forest plot of univariate analysis of intermediate to favorable risk group; **b)** forest plot of univariate analysis of poor to favorable risk group; **c)** forest plot of multivariate analysis of intermediate to favorable risk group; **d)** forest plot of multivariate analysis of poor to favorable risk group.

patients took sorafenib or pazopanib or temsirolimus, the model was efficient to classify favorable and poor-risk group (Supplementary Figure-4).

Multivariate OS

A total of 9 articles (7, 12, 16, 19-22, 25, 26) including 1950 patients in the category, among these patients, 1180 were clear cell RCC and 192 were non clear cell RCC. Kim's article not providing specific number of patients with different pathological types was also included. Favorable, intermediate and poor risk groups had 457, 1122, and 363 patients, respectively.

Intermediate to favorable

The combined HR was 1.32 (95% CI 1.04-1.59) and the forest plot is shown in Figure-3. According to funnel plot and Egger's test (p=0.551), no publication bias was detected. Sensitivity analysis showed the result was not robust. When Cai's article and You's article were omitted respectively, combined HR became not significant. Subgroup analysis showed the model was applicable in Asia. However, in other areas the model could not differentiate patients sufficiently (95% CI 0.80-1.49) (Supplementary Figure-3). Various types of targeted agents from cohort of patients affected the model's effectiveness to classify in favorable and intermediate-risk groups (Supplementary Figure-4).

Poor to favorable

The combined HR was 2.35 (95% CI 1.69-3.01) and the forest plot is shown in Figure-3. According to funnel plot and Egger's test (p=0.555), no publication bias was detected. Sensitivity analysis showed the result was robust. Subgroup analysis showed the model was applicable in both Asia and other areas (Supplementary Figure-3). The model's efficiency was not reliable when it was applied to different types of targeted agents in the cohort of patients (Supplementary Figure-4).

DISCUSSION

IMDC model including six independent factors such as KPS <80%, time from diagnosis to treatment <1 year; hemoglobin <LLN, Calcium >ULN, Neutrophils <ULN, and Platelets >ULN was first set in 2009 (5). After its occurrence, many studies applied it to make risk stratification of patients using targeted agents. However, there was not a systematic evaluation for the model. In-depth analysis of the existing literature was performed to explore the application of IMDC model. Interestingly, it was found that the model was also utilized to predict patient's PFS though it was first set to predict patient's overall survival. Actually, its application in predict patient's PFS had not been explored. This was the first study to validate their application in the area.

Most incorporated articles provide univariate and multivariate analysis of prognostic factors. For meta-analysis, univariate pooling can best reflect potential valuable prognostic factors despite the possibility of combining confounding factors leading to repetitive effects. Multivariate merging may be inherently heterogeneous due to the inconsistencies in the variables included in each article. Conversely, the statistically significant prognostic factors obtained through this combination may be able to withstand the challenges of different conditions and could be widely used.

According to our analysis, IMDC model was able to classify patients to different risk group with various PFS and OS except in the category of intermediate to poor risk group for PFS (95% CI 0.99-1.56). Simultaneously, the combined HR was larger in the category of univariate analysis than those in the category of multivariate analysis. It possibly suggested that IMDC model was affected by other existing factors. In other words, it should be taken into account when the model is incorporated as one independent prognostic factor to reform a new prognostic model. In addition, we also explored the applicability of this model in different drugs and different populations. There are a variety of targeted drugs, and we have included studies that simply use sunitinib as a treatment, as well as a combination of sorafenib, pazopanib, and even mTORi, such as temsirolimus. Based on the subgroup analysis, IMDC model was reliable on the univariate analysis of PFS and OS and multivariate analysis of PFS limited in the poor to favorable risk group. Its applicability was not stable in the category of multivariate analysis of PFS located in the intermediate to favorable risk group

and multivariate analysis of OS. When it came to the area targeted agents were used, various results existed in different conditions. IMDC model was reliable on the univariate analysis of PFS and OS and multivariate analysis of PFS and OS limited in the poor to favorable risk group both in Asia and other areas. It was not reliable in the category of multivariate analysis of PFS located in the intermediate to favorable risk group both in Asia and other areas. However, it could be used in the multivariate analysis of OS in Asia not in other area. There were two main explanations for the difference. On one hand, unstable results were concentrated on the intermediate to favorable risk group, indicating the classification was not accurate enough. On the other hand, PFS results were more stable than OS results, indicating that OS was easier to be affected by other factors other than targeted drug therapy. There was no doubt that the number of studies included is an important factor affecting the outcome. More high-quality clinical studies could provide more robust results.

Limitation and prospection

The findings of this systematic review should be considered in the context of the available evidence, which may be limited by selection bias and follow-up as reflected in the strength of evidence ratings. Due to there was not enough articles available, the application of the model for specific country or race was not explored. Meanwhile, most of the involved patients were ccRCC, the reliability of the model for nccRCC needed more studies to verify. Additionally, most articles used targeted agents as first line therapy except Keizman's, Auclin's and Kwon's articles (6, 16, 26), whether first line or second line of targeted therapy would influence the model was not explored. Although Heng's article (5) showed that there was no difference. And many other targeted agents such as axitinib were not covered in the included studies, leading to that the analysis was not particularly comprehensive. According to our analysis, the number of patients in the intermediate risk group was almost twice that of the other two groups, which was consistent with its initiative results (5). It indicated that a more specific subdivision could be made in the intermediate risk group.

CONCLUSIONS

In summary, our analysis of currently available clinical evidence indicated that IMDC could be applied to classify patients with metastatic renal cell carcinoma using targeted agents. However, different types of targeted agents and various areas could affect the accuracy of the model. There was also a difference in predicting patients' PFS and OS. Based on the limitations of both the studies evaluated and our meta-analysis, further well-designed studies are needed to draw a more definite conclusion as to the clinical significance of IMDC model.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-PelloS, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol. 2019;75:799-810.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.
3. Volpe A, Bollito E, Bozzola C, Di Domenico A, Bertolo R, Zegna L, et al. Classification of Histologic Patterns of Pseudocapsular Invasion in Organ-Confined Renal Cell Carcinoma. Clin Genitourin Cancer. 2016;14:69-75.
4. Powles T, Albiges L, Staehler M, Bensalah K, Dabestani S, Giles RH, et al. Updated European Association of Urology Guidelines Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. Eur Urol. 2017.
5. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27:5794-9.
6. Kwon WA, Cho IC, Yu A, Nam BH, Joung JY, Seo HK, et al. Validation of the MSKCC and Heng risk criteria models for predicting survival in patients with metastatic renal cell carcinoma treated with sunitinib. Ann Surg Oncol. 2013;20:4397-404.
7. Peltola KJ, Penttilä P, Rautiola J, Joensuu H, Hänninen E, Ristimäki A, et al. Correlation of c-Met Expression and Outcome in Patients With Renal Cell Carcinoma Treated With Sunitinib. Clin Genitourin Cancer. 2017;15:487-494.

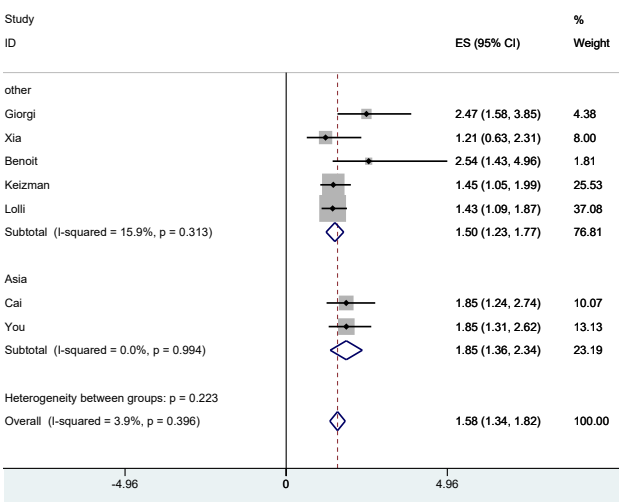
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62:e1-34.
9. GA Wells, B Shea, D O'Connell, J Peterson, V Welch, M Losos, et al. Tugwell,The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.
10. Ioannidis JP, Patsopoulos NA, Evangelou E. Heterogeneity in meta-analyses of genome-wide association investigations. PLoS One. 2007;2:e841.
11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
12. Cai W, Kong W, Dong B, Zhang J, Chen Y, Xue W, et al. Pretreatment Serum Prealbumin as an Independent Prognostic Indicator in Patients With Metastatic Renal Cell Carcinoma Using Tyrosine Kinase Inhibitors as First-Line Target Therapy. Clin Genitourin Cancer. 2017;15:e437-e446.
13. De Giorgi U, Rihawi K, Aieta M, Lo Re G, Sava T, Masini C, et al. Lymphopenia and clinical outcome of elderly patients treated with sunitinib for metastatic renal cell cancer. J Geriatr Oncol. 2014;5:156-63.
14. Beuselinck B, Vano YA, Oudard S, Wolter P, De Smet R, Depoorter L, et al. Prognostic impact of baseline serum C-reactive protein in patients with metastatic renal cell carcinoma (RCC) treated with sunitinib. BJU Int. 2014;114:81-9.
15. Xia Y, Liu L, Xiong Y, Bai Q, Wang J, Xi W, et al. Prognostic value of CC-chemokine receptor seven expression in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitor. BMC Cancer. 2017;17:70.
16. Keizman D, Gottfried M, Ish-Shalom M, Maimon N, Peer A, Neumann A, et al. Active smoking may negatively affect response rate, progression-free survival, and overall survival of patients with metastatic renal cell carcinoma treated with sunitinib. Oncologist. 2014;19:51-60.
17. Kawai Y, Osawa T, Kobayashi K, Inoue R, Yamamoto Y, Matsumoto H, et al. Factors Prognostic for Survival in Japanese Patients Treated with Sunitinib as First-line Therapy for Metastatic Clear Cell Renal Cell Cancer. Asian Pac J Cancer Prev. 2015;16:5687-90.
18. Lolli C, Basso U, Derosa L, Scarpi E, Sava T, Santoni M, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. Oncotarget. 2016;7:54564-54571.
19. You D, Lee C, Jeong IG, Song C, Lee JL, Hong B, et al. Impact of metastasectomy on prognosis in patients treated with targeted therapy for metastatic renal cell carcinoma. J Cancer Res Clin Oncol. 2016;142:2331-8.
20. Miyake M, Kuwada M, Hori S, Morizawa Y, Tatsumi Y, Anai S, et al. The best objective response of target lesions and the incidence of treatment-related hypertension are associated with the survival of patients with metastatic renal cell carcinoma treated with sunitinib: a Japanese retrospective study. BMC Res Notes. 2016;9:79.
21. Lin Z, Liu L, Xia Y, Chen X, Xiong Y, Qu Y, et al. Tumor infiltrating CD19(+) B lymphocytes predict prognostic and therapeutic benefits in metastatic renal cell carcinoma patients treated with tyrosine kinase inhibitors. Oncoimmunology. 2018;7:e1477461.
22. Kim MS, Chung HS, Hwang EC, Jung SI, Kwon DD, Hwang JE, et al. Efficacy of First-Line Targeted Therapy in Real-World Korean Patients with Metastatic Renal Cell Carcinoma: Focus on Sunitinib and Pazopanib. J Korean Med Sci. 2018;33:e325.
23. Wang J, Liu L, Qu Y, Xi W, Xia Y, Bai Q, et al. Prognostic Value of SETD2 Expression in Patients with Metastatic Renal Cell Carcinoma Treated with Tyrosine Kinase Inhibitors. J Urol. 2016;196:1363-1370.
24. Bamias A, Tzannis K, Papatsoris A, Oudard S, Beuselinck B, Escudier B, et al. Prognostic significance of cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma treated with first-line sunitinib: a European multiinstitutional study. Clin Genitourin Cancer. 2014;12:373-83.
25. Yao J, Xi W, Zhu Y, Wang H, Hu X, Guo J. Checkpoint molecule PD-1-assisted CD8(+) T lymphocyte count in tumor microenvironment predicts overall survival of patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. Cancer Manag Res. 2018;10:3419-3431.
26. Auclin E, Bourillon C, De Maio E, By MA, Seddik S, Fournier L, et al. Prediction of Everolimus Toxicity and Prognostic Value of Skeletal Muscle Index in Patients With Metastatic Renal Cell Carcinoma. Clin Genitourin Cancer. 2017;15:350-355.

Correspondence address:
Shuqiu Chen
Zhongda hospital, Southeast University-Urology
87 Dingjiaqiao Road, Nanjing
Nanjing 210009, China
E-mail: chenshuqiuseu@163.com

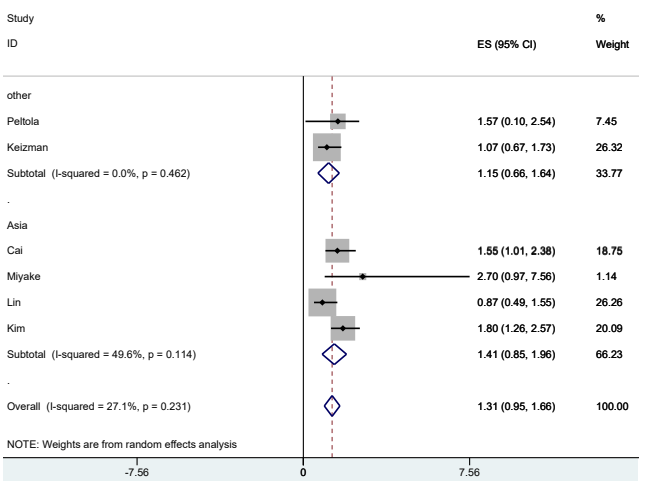
APPENDIX

Supplementary Figure 1 - Subgroup analysis of area for PFS.

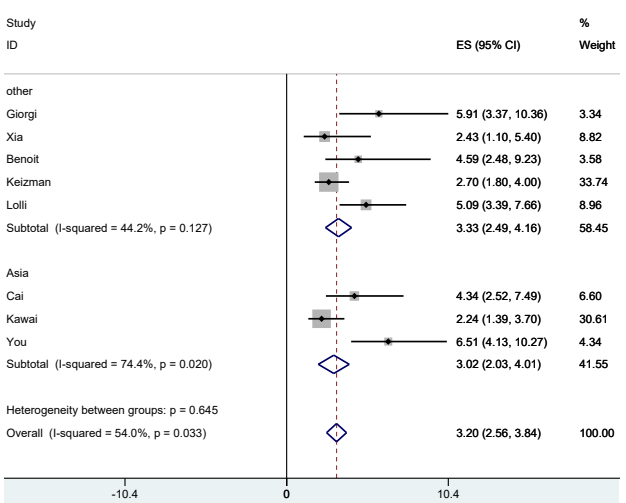
A



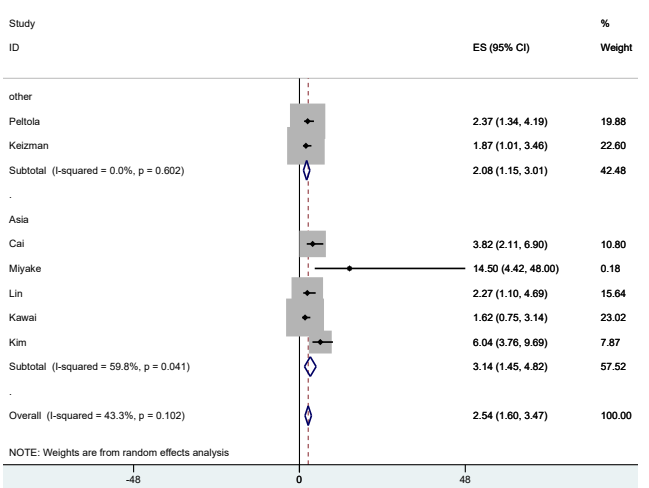
B



C

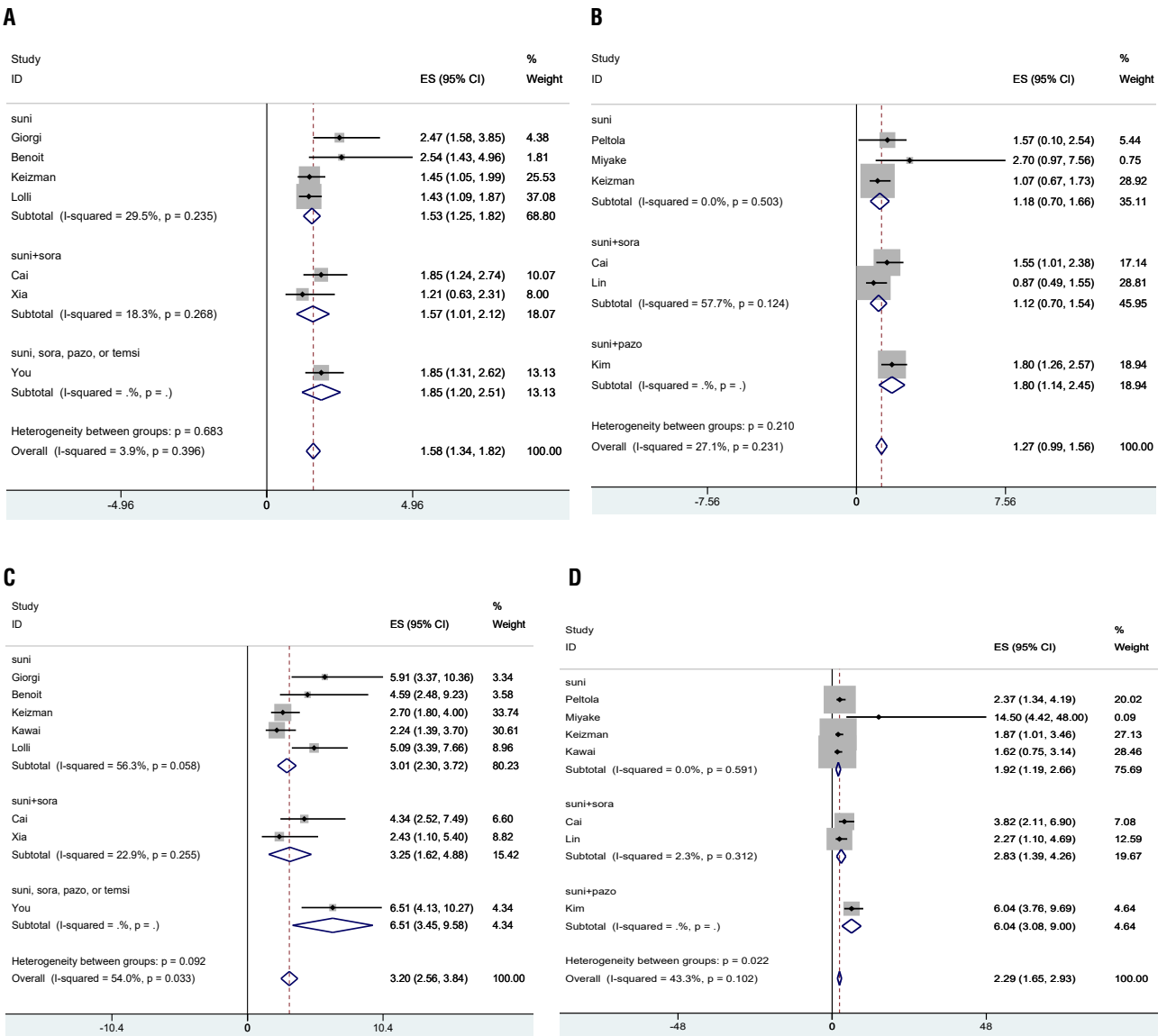


D



a) PFS univariate analysis of intermediate to favorable risk group for area; **b)** PFS univariate analysis of poor to favorable risk group for area; **c)** PFS multivariate analysis of intermediate to favorable risk group for area; **d)** PFS multivariate analysis of poor to favorable risk group for area

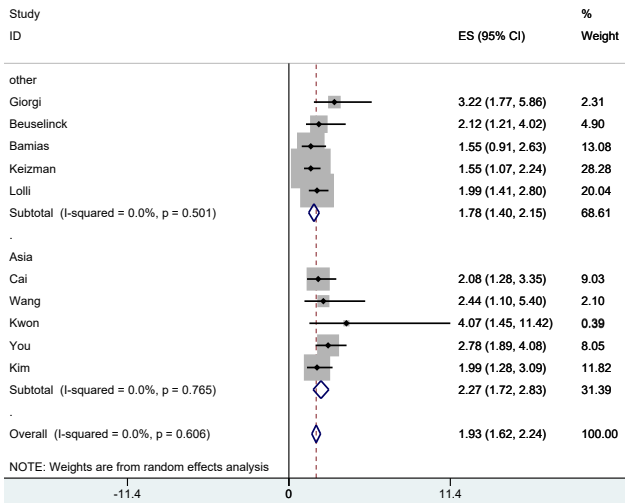
Supplementary Figure 2 - Subgroup analysis of drug type for PFS.



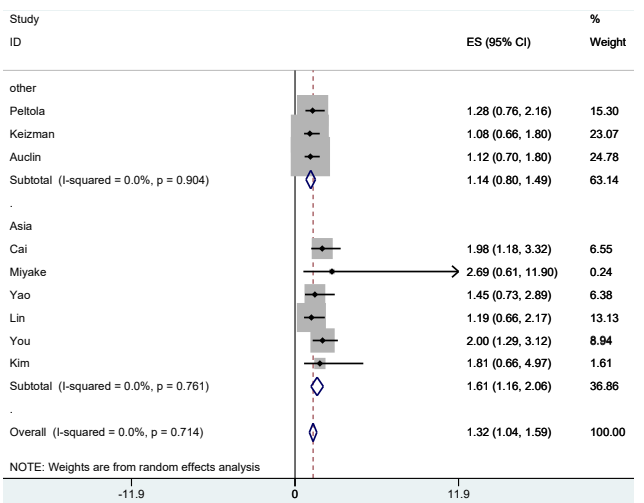
a) PFS univariate analysis of intermediate to favorable risk group for area; **b)** PFS univariate analysis of poor to favorable risk group for area; **c)** PFS multivariate analysis of intermediate to favorable risk group for area; **d)** PFS multivariate analysis of poor to favorable risk group for area

Supplementary Figure 3 - Subgroup analysis of area for OS.

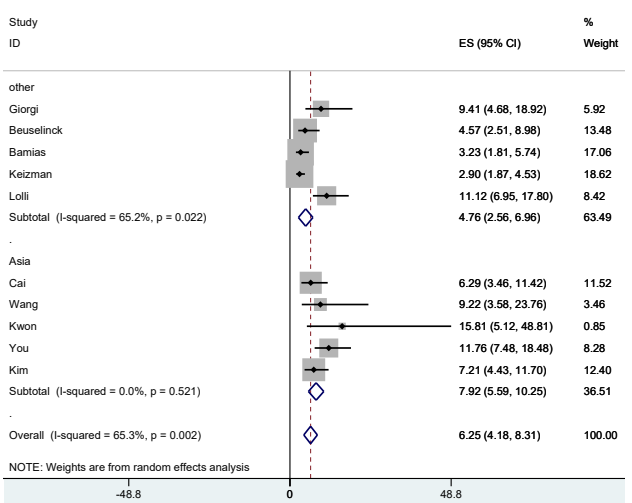
A



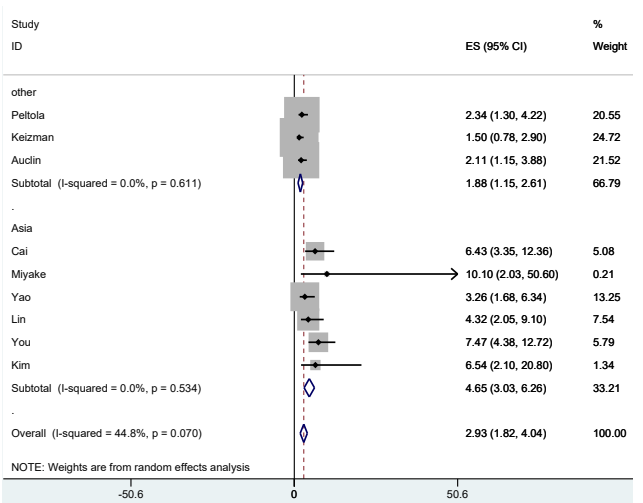
B



C



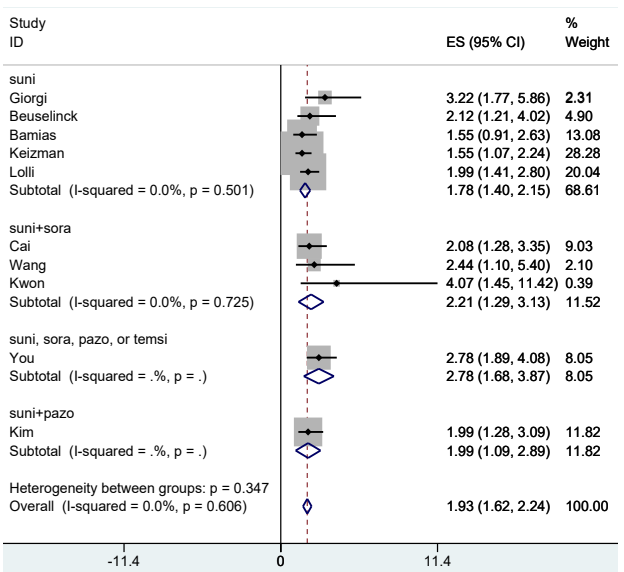
D



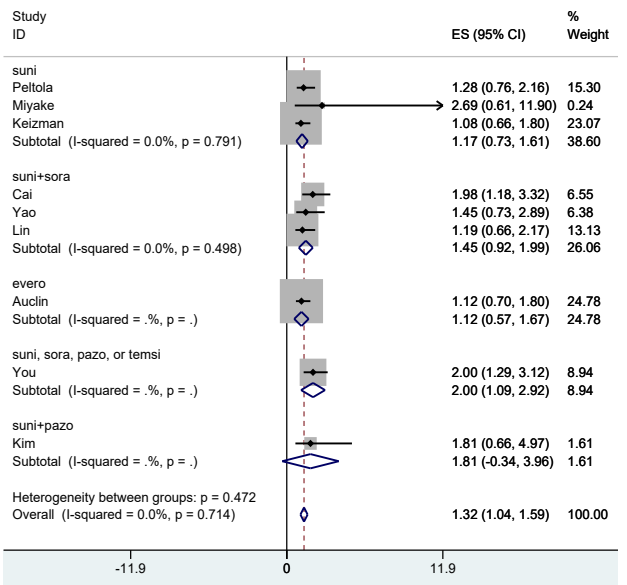
a) OS univariate analysis of intermediate to favorable risk group for area; **b)** OS univariate analysis of poor to favorable risk group for area; **c)** OS multivariate analysis of intermediate to favorable risk group for area; **d)** OS multivariate analysis of poor to favorable risk group for area.

Supplementary Figure 4 - Subgroup analysis of drug type for OS.

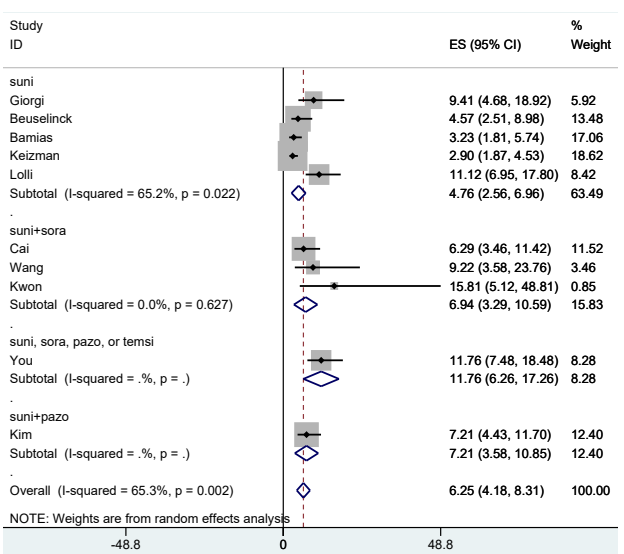
A



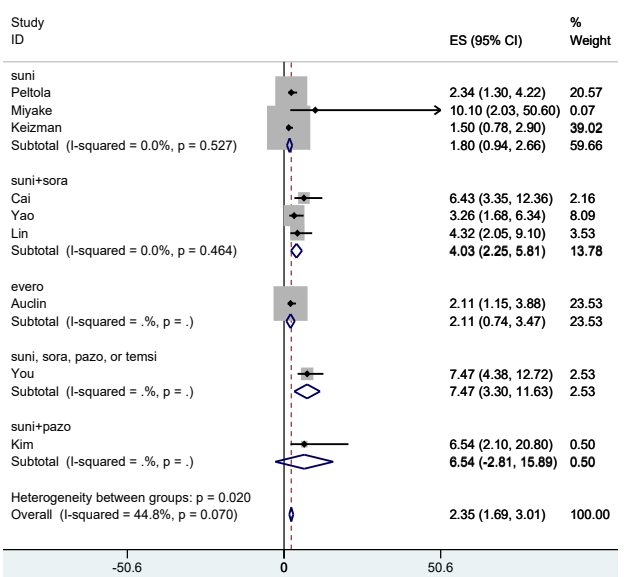
B



C



D



a) OS univariate analysis of intermediate to favorable risk group for area; **b)** OS univariate analysis of poor to favorable risk group for area; **c)** OS multivariate analysis of intermediate to favorable risk group for area; **d)** OS multivariate analysis of poor to favorable risk group for area.

ORIGINAL ARTICLE

Vol. 46 (3): 341-350, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2018.0865

Oncological and functional outcomes of open versus laparoscopic partial nephrectomy in T1b tumors: A single-center analysis

Ibrahim Kartal [1], Nihat Karakoyunlu [1], Çağlar Çakici [1], Osman Karabacak [1], Levent Sağnak [1], Hamit Ersoy [1]

[1] *Department of Urology, University of Health Sciences, Dişkapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey*

ABSTRACT

Purpose: This study aims to evaluate the oncological and functional results of open partial nephrectomy (OPN) and laparoscopic partial nephrectomy (LPN) at the T1b clinical stage, which constitutes 25% of renal cell carcinomas (RCC) at diagnosis.
Materials and Methods: The characteristics of 63 patients with stage T1b solitary tumor who underwent OPN (41) or LPN (22) were compared. The survival analysis was performed using the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were performed to determine the factors affecting disease-free survival. Potential predictive factors, which might affect the postoperative glomerular filtration rate (GFR), were evaluated using multivariate linear regression analysis.
Results: No differences were observed between OPN and LPN groups regarding patient and tumor characteristics. Although the warm ischemia time, intraoperative estimated blood loss, and operation duration were higher in the LPN group, no differences were noted between the two techniques regarding complication rates ($p<0.001$, $p=0.023$, $p\leq0.001$, and $p=0.190$, respectively). The median hospitalization time was shorter in the LPN group than that in the OPN group (4 and 5 days, respectively), with less severe complications. No intergroup differences were observed regarding cancer-specific survival (CSS), disease-free survival (DFS), and overall survival (OS). The evaluation of the factors affecting DFS showed that age was an effective parameter (RR = 1.112, 95% CI: 1.010–8.254), but the surgical technique was not.
Conclusion: No differences were observed between OPN and LPN techniques between oncological and functional outcomes in patients with clinical stage T1b RCC.

ARTICLE INFO

Ibrahim Kartal
http://orcid.org/0000-0002-2313-3522

Keywords:
Carcinoma, Renal Cell; Warm Ischemia; Disease-Free Survival

Int Braz J Urol. 2020; 46: 341-50

Submitted for publication:
December 20, 2018

Accepted after revision:
December 13, 2019

Published as Ahead of Print:
January 15, 2020

INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common malignancies among genitourinary cancers, detected at an early (localized) stage based on the increased incidental diagnosis, and >70% patients are at stage T1. The optimal treatment of localized RCC is surgery (1). Despite satisfactory oncological results of radical nephrectomy for localized RCC, risk was reportedly higher in patients with chronic kidney disease. Therefore, the preservation of renal parenchyma is recommended for stage-T1 tumors to reduce morbidity (2, 3). Compared with radical nephrectomy, partial nephrectomy (PN)

provided better preservation of the renal function and similar oncological outcomes, and therefore, it became the standard treatment for T1 tumors, especially stage T1a, per the guidelines (4, 5).

Despite OPN being the sought-after standard treatment of T1 tumors, technological development and increased preference for minimally--invasive procedures have led to the popularity of the conventional and robot-assisted laparoscopic partial nephrectomy (LPN) in T1 tumors. LPN is generally preferred for T1a tumors. However, >25% RCC cases are determined in the clinical stage T1b (6). Clinicians are using LPN apprehensively for T1b tumors even in cases with an increased tumor size, which may negatively affect the oncological outcomes.

Based on our experience regarding the endourological methods, we evaluated the difference between OPN and conventional LPN in terms of their oncological and functional results in T1b tumors.

MATERIALS AND METHODS

We evaluated the data of 63 patients, who were initially diagnosed with RCC and at clinical stage T1b and underwent OPN (n=41) or LPN (n=22) in our clinic between January 2012 and June 2015. Only patients with solitary tumors were included. Patients with synchronous bilateral, metachronous, multiple ipsilateral tumors, distant metastasis, and hereditary RCC syndrome were excluded. The longest tumor diameter observed in the imaging method was accepted as the tumor size. After the patients were informed, the surgical approach was chosen based on the surgeon's experience and opinion regarding the surgical applicability. Three experienced endourologists performed the laparoscopic interventions. The demographic, intraoperative, and postoperative information were extracted from the designed and updated data.

The renal tumor complexity was calculated using R.E.N.A.L. nephrometry scoring system (radius, exophytic/endophytic, nearness of tumor to collecting system, anterior/posterior, hilar tumor touching main renal artery or vein, and location relative to polar lines) (7).

In both procedures, after the dissection of the perinephric fat tissue following the retainment of the fat tissue only on the tumor, the renal artery and vein were separately clamped as far as possible. The tumor was excised with cold knife and sharp incision after considering a safety margin around the tumor and leaving the renal parenchyma intact. Following the closure of the tumor base and parenchyma, the clamps were quickly released. The adjuvant hemostatic agents were used per the surgeon's preference. The complications were classified based on the modified Clavien classification (8).

The follow-up was performed every 3 months in the first year, every 6 months in the second and third years, and yearly thereon. Abdominal computed tomography was performed at each visit. Magnetic resonance imaging was performed in patients with renal failure or hypersensitivity to contrast agents. DFS, CSS, and OS analyses were performed using the Kaplan-Meier method for each technique followed by an intertechnique comparison. The effects of all risk factors expected to be effective on DFS were evaluated using uni- and multivariate Cox proportional hazard regression method.

Estimated glomerular filtration rate (GFR) and modification of diet in renal disease (MDRD) for each patient were calculated per the equation [eGFR in mL/minute/$1.73m^2$=$186.3 \times (\text{serum creatinine})^{-154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$] (9). The GFR values in the preoperative and postoperative periods (first day, the sixth month, and last visit) were compared. The effects of all potential factors (age, ASA, ischemia time, surgical procedure) on surgery, which may be predictive in the estimation of GFR changes (ΔGFR), were investigated using multivariate linear regression analysis in the sixth postoperative month and at the last visit and compared with the preoperative level.

Statistical analysis

Normal and non-normal distributions of continuous variables were evaluated using the Kolmogorov-Smirnov test. Levene's test was used to assess the homogeneity of variances.

The mean intergroup differences were compared using the Student's t-test, and the Mann-Whitney U test was applied to compare the data with non-normal distribution. The categorical data were analyzed using the continuity corrected Chi-square or Fisher's exact test, where appropriate.

The significance of the correlations between patient characteristics and DFS was assessed using the univariate Cox's proportional hazard regression analyses. The best predictor(s) of DFS were evaluated using the multivariate Cox's proportional hazard regression analysis. The relative risk and 95% confidence intervals were also calculated for each independent variable. DFS, OS, and CSS rates were calculated using the Kaplan-Meier survival analysis, and the surgical techniques were compared using the log-rank test. The 5-year cumulative survival rates with a confidence interval of 95% were calculated for each surgical technique.

The best predictor(s) of ΔGFR were evaluated using the multivariate Cox's proportional hazard regression analysis. Coefficients of regression and 95% confidence interval were also calculated for each independent variable.

Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). A p value of less than 0.05 was considered statistically significant. However, Bonferroni correction was applied for all possible multiple comparisons to control type I error.

RESULTS

No statistically significant differences were noted between the OPN and LPN groups, treated at the clinical stage T1b and concordant with the criteria regarding the mean age, gender distribution, localization, mean BMI, ASA score, median tumor size, and median R.E.N.A.L. score ($p>0.05$; Table-1).

The median values of WIT, estimated blood loss, and operation duration were significantly higher in the LPN group than in the OPN group ($p<0.001$, $p=0.023$, $p<0.001$, respectively).

Table 1 - Preoperative characteristics of patients and tumors according to surgical procedures.

	OPN (n = 41)	LPN (n = 22)	p-value
Age (year), mean	58.2 ± 10.7	52.7 ± 11.1	0.061[a]
Gender (n), %			0.999[b]
Male	25 (61.0%)	14 (63.6%)	
Female	16 (39.0%)	8 (36.4%)	
Side (n), %			0.740[b]
Right	21 (51.2%)	13 (59.1%)	
Left	20 (48.8%)	9 (40.9%)	
BMI (kg/m^2), mean	27.5 ± 3.3	25.9 ± 3.0	0.064[a]
ASA score (n), %			0.205[b]
I–II	28 (68.3%)	19 (86.4%)	
III–IV	13 (31.7%)	3 (13.6%)	
Tumor size (mm), median	51.0 (41.0–74.0)	47.5 (42.0–75.0)	0.236[c]
R.E.N.A.L score (median)	8.0 (5.0–11.0)	8.0 (6.0–10.0)	0.188[c]

OPN = Open partial nephrectomy; **LPN =** Laparoscopic partial nephrectomy; **BMI =** Body mass index; **ASA =** American Society of Anesthesiologists; **R.E.N.A.L =** Radius, exophytic/endophytic, nearness of tumor to collecting system, anterior/posterior, hilar tumor touching main renal artery or vein and location relative to polar lines); **a =** Student's t-test; **b =** Continuity Corrected Chi-square test; **c =** Mann–Whitney U test.

No significant intergroup differences were observed regarding intraoperative erythrocyte suspension transfusion, operation duration, hospitalization time, postoperative complication rate, grade distribution among the patients with complication, pathological assessment, Fuhrman nuclear grade, positive surgical margin, follow-up time, and mortality (p>0.05). Regarding the intraoperative complications, a pleural injury occurred in two patients who underwent OPN treated with primary suturing during the operation (Table-2).

All treatment modalities were successfully applied during the perioperative period, and no operation-associated mortality was observed. Six complications occurred in OPN group (14.6%) and seven in the LPN group (31.8%). Despite the lower

Table 2 - Perioperative and postoperative results according to the surgical technique.

	OPN (n = 41)	LPN (n = 22)	p-value
Warm ischemia time (min), median	16.0 (5.0-27.0)	25.5 (5.0-60.0)	**<0.001**[a]
Estimated blood loss (mL), median	250 (100-1850)	400 (100-1200)	**0.023**[a]
Intraoperative ES transfusion, (pack), median	0 (0-4)	0 (0-6)	0.112[a]
Duration of operation (min), median	120 (60–180)	155 (90–240)	**<0.001**[a]
Hospitalization time (day), median	5 (2–16)	4 (3–7)	0.221[a]
Intraoperative pleural injury (n), %	2 (4.9%)	0 (0.0%)	0.538[b]
Postoperative complications (n), %	6 (14.6%)	7 (31.8%)	0.190[b]
Postoperative complications (n), %			0.103[b]
Grade < 3	1 (16.7%)	5 (71.4%)	
Grade ≥ 3	5 (83.3%)	2 (28.6%)	
Wound site infection	1 (2.4%)	1 (4.5%)	0.999[b]
Urine leakage	3 (7.3%)	3 (13.6%)	0.413[b]
Blood transfusion	0 (0.0%)	2 (9.1%)	0.118[b]
Prolonged ileus	0 (0.0%)	1 (4.5%)	0.349[b]
Re-operation due to bleeding	2 (4.9%)	0 (0.0%)	0.538[b]
Pathologic evaluation (n), %			
Benign	3 (7.3%)	3 (13.6%)	0.413[b]
Clear Cell Ca	31 (75.6%)	17 (77.3%)	0.999[c]
Non-Clear Cell Ca	7 (17.1%)	2 (9.1%)	0.476[b]
Fuhrman nuclear grade (n), %			0.478[b]
Grade I–II	32 (84.2%)	14 (73.7%)	
Grade III–IV	6 (15.8%)	5 (26.3%)	
Surgical margin positivity (n), %	2 (4.9%)	2 (9.1%)	0.606[b]
Follow-up time (month), median	54 (37–78)	62 (27–78)	0.471[a]
Death (n), %	4 (9.8%)	2 (9.1%)	0.999[b]
Oncological	2 (4.9%)	1 (4.5%)	0.999[b]
Non-oncological	2 (4.9%)	1 (4.5%)	0.999[b]

a = Mann–Whitney U test; **b =** Fisher's exact test; **c =** Continuity Corrected Chi-square test; **ES =** Erythrocyte suspension.

complication rate in the OPN group, major complications (grade 3) were observed in five patients (two were re-operated owing to bleeding).

In the OPN group, urinary leakage was observed and treated using ureteral stents in three patients, of which one patient continued to have urinary leakage despite stent insertion and was eventually treated with percutaneous nephrostomy.

In the LPN group, two patients required transfusion owing to low postoperative hemoglobin level. One patient had prolonged ileus, which resolved during the follow-up. Besides, two patients developed urinary leakage, of which the one with grade 1 leakage regressed during the follow-up, and the other one with grade 3a leakage was treated with a ureteral stent.

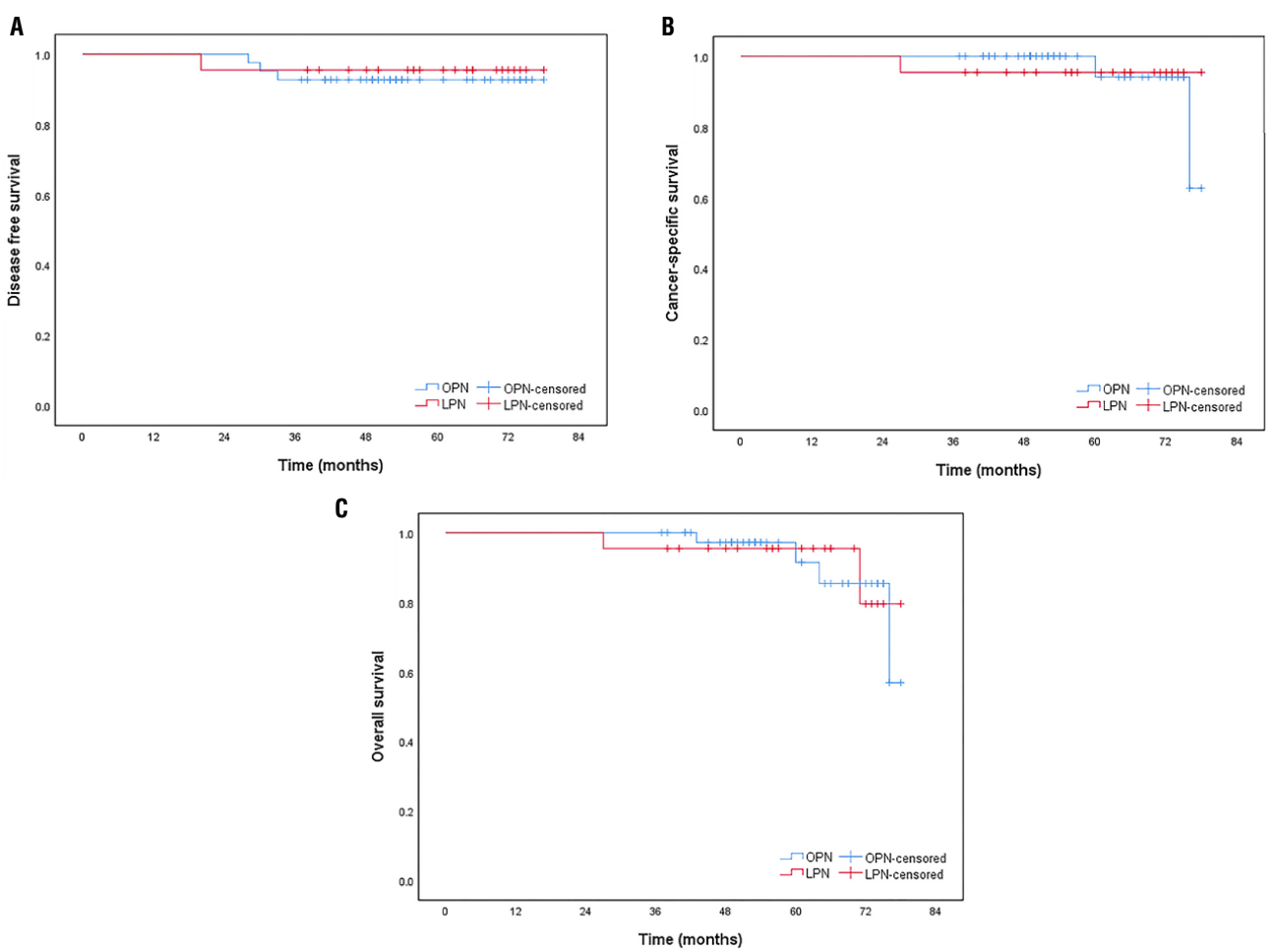
Pathological results were benign in three LPN (13.6%) and three OPN (7.3%) patients. Positive surgical margin was detected in two patients of each group (OPN: 4.8%, LPN: 9.1%). No recurrence was observed in these four patients.

Median follow-up time was 54 (37-78) and 62 (27-78) months for OPN and LPN groups, (p=0.471), respectively. The 5-year DFS rate was 92.7% (95% CI: 70.7-78.3) in the OPN and 95.5% (70.3-80.4) in the LPN group. No statistically significant intergroup difference was observed regarding DFS (log-rank=0.161 and p=0.688).

The 5-year CSS rate was 94.1% (95% CI: 74.1-78.5) in the OPN and 95.5% (71.2-80.1) in the LPN group with no statistically significant intergroup difference (log-rank=0.001 and p=0.987).

The 5-year OS rate was 91.5% (95% CI: 71.5-77.6) in the OPN and 95.5% (69.8-79.3) in the LPN group with no statistically significant intergroup difference (log-rank=0.013 and p=0.909, Figure-1).

Figure 1 - Disease-free survival (a), cancer-specific survival (b), overall survival (c) according to the surgical techniques.



Two patients in the OPN and one patient in the LPN group relapsed, and all three died. The two patients of the OPN group died because of cardiac disorders after the fifth postoperative year, and the one patient from the LPN group with multiple comorbidities also died because of cardiac disease.

The univariate statistical analysis showed no significant difference between tumor size, surgical procedure, pathology, Fuhrman nuclear grade, R.E.N.A.L. score, and DFS (p>0.05). However, with the univariate analysis, we determined that the rate of recurrence increased significantly with age (RR=1.108, 95% CI: 1.006-1.220 and p=0.037). Furthermore, multivariate Cox proportional hazard regression analysis revealed that age was effective on the DFS irrespective of other factors. Each 10-year increase in age caused a statistically significant increase (2.891 times) in the development of recurrence regardless of other factors (95% CI: 1.010-8.254, Table-3).

The intergroup differences regarding mean GFR measurements, according to Bonferroni correction, were considered significant with p<0.0125, within the follow-up period. No significant differences were observed between the groups regarding GFR levels in the preoperative, first postoperative day, the sixth month, and the last visit, although GFR had an elevated course in the LPN group (p>0.0125).

The ΔGFR on the first postoperative day, sixth month, and last visit compared with the preoperative level was considered significant with p<0.0083 per the Bonferroni correction. No significant intergroup difference was observed regarding the first day, the sixth month, and last visit ΔGFR level compared with the preoperative level per the Bonferroni correction (p>0.0083; Table-4).

All potential factors (age, ASA, ischemia time, surgical procedure)-considered predictive for ΔGFR on the first postoperative day compared with the preoperative period-did not have any significant positive predictive value (p>0.05).

In addition, none of the factors mentioned above had any significant predictive value in the sixth postoperative month (p>0.05). After the correction according to other factors, we determined that prolonged ischemia time caused a significant decrease in GFR level in the sixth postoperative month (B=-0.297, 95% CI: -0.558-0.036 and p=0.026).

All the potential factors thought to be effective on the prediction of ΔGFR were found to have no positive predictive value (p>0.05) at the last follow-up visit. We concluded that only the duration of the ischemia might have some effect on the sixth postoperative month (Table-5). One patient who underwent OPN with a preoperative GFR of 56mL/min/1.73m^2 and had concomitant diabetes mellitus required hemodialysis in the fourth postoperative year.

DISCUSSION

Several studies have focused on the comparison of the long-term results of LPN and OPN in

Table 3 - Results of the univariate and multivariate Cox regression analysis of the factors that may affect the disease-free survival.

	Univariate			Multivariate		
	RR	95% CI	p-value	RR	95% CI	p-value
Age	1.108	1.006-1.220	**0.037**	1.112	1.001-1.235	**0.049**
Tumor size	1.019	0.921-1.129	0.711	1.023	0.912-1.149	0.694
LPN	0.690	0.066-6.070	0.690	0.812	0.069-9.614	0.869
Non-clear cell Ca	$1,158	0.120-11.132	0.899	1.349	0.130-13.960	0.802
Fuhrman grade	1.968	0.305-12.689	0.476	1.527	0.180-12.991	0.698
R.E.N.A.L. score	0.712	0.300-1.691	0.441	0.666	0.210-2.109	0.490

RR = Relative Risk; **CI =** Confidence Interval; **LPN =** Laparoscopic partial nephrectomy; **Ca =** Carcinoma

Table 4 - Effects of open and laparoscopic partial nephrectomy on renal function

	OPN (n = 41)	LPN (n = 22)	p-value [a]
GFR measurements			
Preoperative	83.71 ± 23.41	95.67 ± 28.20	0.077[b]
Postoperative 1st day	81.15 ± 25.33	89.49 ± 29.11	0.241[b]
Postoperative 6th month	72.49 ± 22.91	86.68 ± 27.50	0.033[b]
Final control	67.51 ± 23.49	84.18 ± 26.92	0.013[b]
Δ GFR			
Postoperative 1st day	–2.56 ± 12.08	–6.18 ± 10.99	0.248[c]
Postoperative 6th month	–11.22 ± 9.68	–8.99 ± 5.89	0.329[c]
Final control*	–16.20 ± 11.23	–11.49 ± 5.80	0.032[c]

***** = Average follow-up period=4.8 years; **OPN =** Open partial nephrectomy; **LPN =** Laparoscopic partial nephrectomy; **GFR =** Glomerular filtration rate; **Δ GFR =** Change in glomerular filtration rate, MDRD GFR (mL/min/1.73 m2); **a =** Student's t-test; **b =** According to the Bonferroni Correction, a p value less than 0.0125 was considered as statistically significant; **c =** According to the Bonferroni Correction, a p value less than 0.0083 was considered as statistically significant.

Table 5 - Multivariate linear regression analysis of potential predictive factors, which may affect the decrease in postoperative MDRD GFR

	Coefficient of regression (B)	95% CI for B		p-value
		Lower limit	Upper limit	
Δ GFR 1st day				
Age	–0.139	–0.457	0.179	0.386
ASA	–2.624	–7.640	2.392	0.299
Ischemia time	–0.209	–0.573	0.155	0.255
OPN	3.999	–3.273	11.270	0.276
Δ GFR 6th month				
Age	–0.089	–0.317	0.139	0.436
ASA	–1565	–5.158	2.028	0.387
Ischemia time	–0.297	–0.558	–0.036	**0.026**
OPN	–3.487	–8.696	1.721	0.185
Δ GFR final control				
Age	–0.051	–0.311	0.209	0.695
ASA	–2.602	–6.695	1.490	0.208
Ischemia time	–0.296	–0.593	0.001	0.051
OPN	–5.585	–11.518	0.348	0.065

*** =** Average follow-up period: 4.8 years; **CI =** Confidence Interval; **ASA =** American Society of Anesthesiologist; **GFR =** Glomerular Filtration Rate; **CI GFR =** Change in Glomerular filtration rate; **OPN =** Open Partial Nephrectomy.

all T1 patients without particularly distinguishing between T1a or T1b. However, to the best of our knowledge, no other study has focused on the comparison of OPN and conventional LPN in T1b tumors. The studies that reported LPN results in T1b patients were typically comparing the results of the laparoscopic procedures in T1a patients (10-12).

Although LPN provides satisfying oncological results in tumors larger than 4cm per the report of Rais-Bahrami et al., the complication rate was higher and the hospitalization time was longer in the T1a group in this study (10). Rezaetalab et al. reported that patient satisfaction was higher, and narcotic analgesia requirement was lower in patients who underwent LPN (13). However, Becker et al. emphasized on the improved recovery time with LPN in T1 tumors and reported that there was no difference between OPN and LPN regarding the perioperative complication rates and long-term quality of life parameters (14). Our results demonstrated that laparoscopy was advantageous in nephron-sparing surgery. Although the complication rate was higher in our LPN group, the major complications were common in OPN group. Studies on PN have indicated shorter hospital stay for patients undergoing laparoscopy (15, 16). However, the reasons for not finding any differences in hospital stay between OPN and LPN in this study are probably because of our vast experience in OPN and slightly higher complication rates in LPN. Moreover, the tumors examined in previous studies were smaller in size, but our study included cases like T1b, wherein LPN was more challenging, which may have led to prolonged hospital stay in LPN cases compared with studies involving smaller-size tumors. Nonetheless, we believe that the length of hospital stay in LPN can be shortened with an increase in experience and appropriate patient selection.

However, LPN is known to be a relatively more difficult technique (17, 18). Despite three experienced endourologists in our clinic performing LPN, WIT, operation duration, and estimated blood loss were better in patients who underwent OPN, which was performed by several surgeons with different experience levels. Despite its technical difficulty, LPN has several advantages like reducing venous bleeding owing to pneumoperitoneum, providing better suturing under vision magnification, and facilitating the coagulation of small vessels (19). Marszalek et al. reported the opposite results and stated that WIT was shorter in LPN compared with OPN (16). The perioperative success with LPN solely depends on the surgeon's experience. Although it could be expected that LPN might be beneficial regarding WIT because of pneumoperitoneum, WIT was longer in the LPN than the OPN group in our study. Notably, some studies have reported shorter WIT in LPN. Nevertheless, we believe that our conflicting results are based on the larger tumor sizes and higher mean R.E.N.A.L. scores. Also, theoretically, the surgical approach is generally more difficult, as tumors with a size between 4 and 7cm may be more complicated and centrally located. A study by Simmons et al. reported that the transperitoneal approach was preferred mostly in stage T1b owing to the large tumor size and the need for pelvicalyceal repair and the rate of heminephrectomy was increased. Despite this, no difference was observed regarding intraoperative and perioperative complications compared with the smaller tumor (12). We obtained similar results in our study, and we observed only increases in the estimated blood loss and operation duration. If ever there was a significant difference in these values, it was not reflected in the complication rates.

Although the significance of SMP in the nephron-sparing surgery is still under debate, an increase may be seen in the LPN group because of the difficulty of the technique. Although it was somewhat difficult to assess SMP in our LPN group because of the small subject size, the SMP rate was higher in this group. The clear cell carcinoma evaluation of two patients (9.1%), who underwent LPN, displayed SMP but no recurrence was observed in these two patients during the 5-year follow-up period. In a recently published study, the investigators did not find a difference regarding SMP between laparoscopic, robot-assisted, and open techniques carried out in patients with T1b and T2a tumors, and they also reported that the stage of the tumor did not have any effect on SMP (20).

Several studies have reported low morbidity rates, suitable cost-effectiveness, and satisfying oncological results for laparoscopic PN (15, 21, 22). In the study conducted by Springer et al., OPN and LPN were performed in the treatment of T1 tumors, and the 5-year OS and CSS rates were 92% versus 94% and 88% versus 91% respectively (23). Lane et al. conducted a study focused on T1 tumors, and the separate evaluation of the T1b tumor showed that the 10-year DFS rate was 90% in patients who underwent LPN (24). In another study, 46 T1b patients were operated using robot-assisted LPN and the OS, DFS, and CSS rates were 97.1%, 97.1%, and 100%, respectively, after a 24.3-month follow-up (25). In our study, after a mean follow-up period of 58.1 [37-78] months, we concluded that OPN and LPN provided comparable oncological outcomes.

The oncological and functional outcomes should be reviewed during the selection of the surgical method for PN considering the increase in morbidity as a result of the decrease in renal functions. Despite the literature reporting that renal function impairment started with lesser than 20 minutes WIT and our intergroup difference regarding WIT, no difference was observed between short-term and long-term Δ GFR values (26). In our study, the analysis of the factors that might affect ΔGFR in long-term showed that only ischemia time was effective.

The limitations of our study were the retrospective design, small subject size, and the single-center outcome analysis. Moreover, LPN was performed only in selected patients owing to its implementation difficulty. We acknowledge the fact that drawing a meaningful comparison is difficult in such a small cohort. Although our clinic is a tertiary center, performing LPN and collecting more patients is difficult because of the challenging nature of LPN for tumors >4cm. We believe that our data could add up to the available literature and contribute to designing a meta-analysis.

The number of LPN is increasing with the increase in our experience, and we may be able to conduct randomized-controlled studies in the future. Patient data were collected prospectively in a newly designed database, with the plan of publishing the 10-year results. Further prospective, randomized, and controlled studies are needed to confirm that LPN provides oncological and functional outcomes similar to OPN in T1b tumors and it can be safely performed in T1b tumors because of the beneficial perioperative morbidity rates.

CONCLUSIONS

Treatment of T1b RCC with OPN and LPN provide similar oncological and functional results in the long term. Nevertheless, more minor complications are observed in patients who underwent LPN. Technological advancement and experience have made LPN advantageous in terms of short hospitalization time and faster recovery process compared with OPN. However, considering its technical difficulty, LPN should be performed only in selected patients at experienced and high-capacity health centers.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst. 2006;98:1331-4.
2. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol. 2017;198:520-9.
3. Capitanio U, Terrone C, Antonelli A, Minervini A, Volpe A, Furlan M, et al. Nephron-sparing techniques independently decrease the risk of cardiovascular events relative to radical nephrectomy in patients with a T1a-T1b renal mass and normal preoperative renal function. Eur Urol. 2015;67:683-9.
4. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67:913-24.
5. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. J Urol. 2009;182:1271-9.
6. Karakiewicz PI, Lewinshtein DJ, Chun FK, Briganti A, Guille F, Perrotte P, et al. Tumor size improves the accuracy of TNM predictions inpatients with renal cancer. Eur Urol. 2006;50:521-8.

7. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182:844-53.
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.
9. Lucas SM, Stern JM, Adibi M, Zeltser IS, Cadeddu JA, Raj GV. Renal function outcomes in patients treated for renal masses smaller than 4 cm by ablative and extirpative techniques. J Urol. 2008;179:75-9.
10. Rais-Bahrami S, Romero FR, Lima GC, Kohanim S, Permpongkosol S, Trock BJ, et al. Elective laparoscopic partial nephrectomy in patients with tumors >4 cm. Urology. 2008;72:580-3.
11. Lifshitz DA, Shikanov SA, Deklaj T, Katz MH, Zorn KC, Shalhav AL. Laparoscopic partial nephrectomy for tumors larger than 4 cm: a comparative study. J Endourol. 2010;24:49-55.
12. Simmons MN, Chung BI, Gill IS. Perioperative efficacy of laparoscopic partial nephrectomy for tumors larger than 4 cm. Eur Urol. 2009;55:199-207.
13. Rezaeetalab GH, Karami H, Dadkhah F, Simforoosh N, Shakhssalim N. Laparoscopic Versus Open Partial Nephrectomy for Stage T1a of Renal Tumors. Urol J. 2016;13:2903-7.
14. Becker A, Pradel L, Kluth L, Schmid M, Eichelberg C, Ahyai S, et al. Laparoscopic versus open partial nephrectomy for clinical T1 renal masses: no impact of surgical approach on perioperative complications and long-term postoperative quality of life. World J Urol. 2015;33:421-6.
15. Permpongkosol S, Bagga HS, Romero FR, Sroka M, Jarrett TW, Kavoussi LR. Laparoscopic versus open partial nephrectomy for the treatment of pathological T1N0M0 renal cell carcinoma: a 5-year survival rate. J Urol. 2006;176:1984-8.
16. Marszalek M, Meixl H, Polajnar M, Rauchenwald M, Jeschke K, Madersbacher S. Laparoscopic and open partial nephrectomy: a matched-pair comparison of 200 patients. Eur Urol. 2009;55:1171-8.
17. Porpiglia F, Bertolo R, Amparore D, Fiori C. Margins, ischaemia and complications rate after laparoscopic partial nephrectomy: impact of learning curve and tumour anatomical characteristics. BJU Int. 2013;112:1125-32.
18. Hanzly M, Frederick A, Creighton T, Atwood K, Mehedint D, Kauffman EC, et al. Learning curves for robot-assisted and laparoscopic partial nephrectomy. J Endourol. 2015;29:297-303.
19. Porpiglia F, Mari A, Bertolo R, Antonelli A, Bianchi G, Fidanza F, et al. Partial Nephrectomy in Clinical T1b Renal Tumors: Multicenter Comparative Study of Open, Laparoscopic and Robot-assisted Approach (the RECORd Project). Urology. 2016;89:45-51.
20. Ayangbesan A, Golombos DM, Golan R, O'Malley P, Lewicki P, Wu X, et al. Surgical Approach Does Not Impact Margin Status After Partial Nephrectomy for Large Renal Masses. J Endourol. 2019;33:50-60.
21. Allaf ME, Bhayani SB, Rogers C, Varkarakis I, Link RE, Inagaki T, et al. Laparoscopic partial nephrectomy: evaluation of long-term oncological outcome. J Urol. 2004;172:871-3.
22. Qian J, Li P, Qin C, Zhang S, Bao M, Liang C, et al. Laparoscopic Partial Nephrectomy with Precise Segmental Renal Artery Clamping for Clinical T1b Tumors. J Endourol. 2015;29:1386-91.
23. Springer C, Hoda MR, Fajkovic H, Pini G, Mohammed N, Fornara P, et al. Laparoscopic vs open partial nephrectomy for T1 renal tumours: evaluation of long-term oncological and functional outcomes in 340 patients. BJU Int. 2013;111:281-8.
24. Lane BR, Campbell SC, Gill IS. 10-year oncologic outcomes after laparoscopic and open partial nephrectomy. J Urol. 2013;190:44-9.
25. Maddox M, Mandava S, Liu J, Boonjindasup A, Lee BR. Robotic partial nephrectomy for clinical stage T1b tumors: intermediate oncologic and functional outcomes. Clin Genitourin Cancer. 2015;13:94-9.
26. Simmons MN, Schreiber MJ, Gill IS. Surgical renal ischemia: a contemporary overview. J Urol. 2008;180:19-30.

Correspondence address:
Ibrahim Guven Kartal, MD
Department of Urology,
University of Health Sciences,
Dişkapi Yildirim Beyazit Training and
Research Hospital
Ankara, 06110, Turkey
Phone: + 905556298424
Email: ibrahimguvenkartal@gmail.com

EDITORIAL COMMENT

Vol. 46 (3): 351-352, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2018.0865.1

Editorial Comment: Oncological and functional outcomes of open versus laparoscopic partial nephrectomy in T1b tumors: A single-center analysis

Luciano A. Favorito [1, 2]

[1] Professor Associado da Unidade de Pesquisa Urogenital - Universidade do Estado de Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil, [2] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil

COMMENT

Kartal and Collegues from Turkey in this important paper studied the oncological and functional results of open partial nephrectomy (OPN) and laparoscopic partial nephrectomy (LPN) at the T1b clinical stage in 63 patients and compared 41 submitted to OPN and 22 submitted to LPN (1). The authors observed that there are no differences between OPN and LPN techniques between oncological and functional outcomes in patients with clinical stage T1b RCC.

Partial nephrectomy (open, laparoscopic or robotic) is considered the gold standard for treating localized renal tumors (2-6). In last years important technical improvements were introduced with robotic surgery. Recently a interesting study suggested that the robotic technique is a valid option for partial nephrectomy, especially for PADUA<10 lesions but without differences between surgical techniques in more complex masses (7). The present paper confirms previous findings (8-10) that open and laparoscopic surgery still has indications in complex cases and (because the robotic costs) in countries in development.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Kartal I, Karakoyunlu N, Çakici Ç, Karabacak O, Sağnak L, Ersoy H. Oncological and functional outcomes of open versus laparoscopic partial nephrectomy in T1b tumors: A single-center analysis. Int Braz J Urol. 2020;46: 341-50.
2. Volpe A, Cadeddu JA, Cestari A, Gill IS, Jewett MA, Joniau S, et al. Contemporary management of small renal masses. Eur Urol. 2011;60:501-15.
3. Porreca A, D'Agostino D, Dente D, Dandrea M, Salvaggio A, Cappa E, et al. Retroperitoneal approach for robot-assisted partial nephrectomy: technique and early outcomes. Int Braz J Urol. 2018;44:63-8.
4. Lanchon C, Arnoux V, Fiard G, Descotes JL, Rambeaud JJ, Lefrancq JB, et al. Super-selective robot-assisted partial nephrectomy using near-infrared flurorescence versus early-unclamping of the renal artery: results of a prospective matched-pair analysis. Int Braz J Urol. 2018;44:53-62.
5. Tachibana H, Takagi T, Kondo T, Ishida H, Tanabe K. Comparison of perioperative outcomes with or without renorrhaphy during open partial nephrectomy: A propensity score-matched analysis. Int Braz J Urol. 2018;44:467-74.
6. Bertolo R, Fiori C, Piramide F, Amparore D, Porpiglia F. The preoperative stratification of patients based on renal scan data is unable to predict the functional outcome after partial nephrectomy. Int Braz J Urol. 2018;44:740-9.

7. Bravi CA, Larcher A, Capitanio U, Mari A, Antonelli A, Artibani W, et al. Perioperative Outcomes of Open, Laparoscopic, and Robotic Partial Nephrectomy: A Prospective Multicenter Observational Study (The RECORd 2 Project). Eur Urol Focus. 2019;11. pii: S2405-4569(19)30335-9. [Epub ahead of print].
8. Zapala P, Dybowski B, Miazek N, Radziszewski P. Open partial nephrectomy for entirely intraparenchymal tumors: a matched case-control study of oncologic outcome and complication rate. Int Braz J Urol. 2017;43:209-15.
9. Tsivian M, Tsivian E, Stanevsky Y, Bass R, Sidi AA, Tsivian A. Laparoscopic partial nephrectomy for tumors 7cm and above. Perioperative outcomes. Int Braz J Urol. 2017;43:857-62.
10. Kaygisiz O, Çelen S, Vuruşkan BA, Vuruşkan H. Comparison of two different suture techniques in laparoscopic partial nephrectomy. Int Braz J Urol. 2017;43:863-70.

ARTICLE INFO

Luciano A. Favorito
http://orcid.org/0000-0003-1562-6068

Int Braz J Urol. 2020; 46: 351-2

Luciano A. Favorito, MD, PhD

Unidade de Pesquisa Urogenital
da Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

Submitted for publication:
January 30, 2020

Accepted after revision:
February 05, 2020

ORIGINAL ARTICLE

Vol. 46 (3): 353-362, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0011

Evaluation of nuclear NF-κB, transglutaminase2, and ERCC1 as predictors of platinum resistance in testicular tumors

Alan A. Azambuja [1], Paula Engroff [2], Bruna T. Silva [3], Roberta C. S. Zorzetti [3], Fernanda B. Morrone [4]

[1] Programa de Pós-Graduação em Medicina e Ciências da Saúde, Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, PUCRS e Hospital Mãe de Deus, Porto Alegre, Brasil; [2] Instituto de Geriatria e Gerontologia, Pontifícia Universidade Católica do Rio Grande do Sul, PUCRS, Porto Alegre, Brasil; [3] Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, PUCRS, Porto Alegre, Brasil; [4] Programa de Pós-Graduação em Medicina e Ciências da Saúde, Escola de Medicina e Laboratório de Farmacologia Aplicada, Escola de Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brasil

ABSTRACT

Purpose: Testicular germ cells tumor (TGCT) are associated with a high cure rate and are treated with platinum-based chemotherapy. However, a group of testicular cancer patients may have a very unfavorable evolution and insensitivity to the main therapeutic agent chemotherapy (CT) cisplatin. The aim of this study was to evaluate the risk of recurrence and overall survival related to the expression of nuclear factor kappa-B (NF-κB), transglutaminase 2 (TG2) and excision repair cross-complementation group 1 (ERCC1) in patients with TGCT treated with platinum combinations.

Patients and Methods: A retrospective study was performed with TGCT patients treated with platinum-based chemotherapy. Immunohistochemical analysis was performed and the expression was correlated with clinical and laboratory data.

Results: Fifty patients were included, the mean age was 28.4 years (18 to 45), and 76% were non-seminoma. All patients were treated with standard cisplatin, etoposide and bleomycin or cisplatin, and etoposide. Patient's analyzed immunodetection for NF-κB, TG2, and ERCC1 were positive in 76%, 54% and 42%, respectively. Multivariate analysis identified that positive expressions to ERCC1 and NF-κB are independent risk factors for higher recurrence TGCT after chemotherapy (RR 2.96 and 3.16, respectively). Patients with positive expression of ERCC1 presented a poor overall survival rate for 10-year follow (p=0.001).

Conclusions: The expression of ERCC1 and NF-κB give a worse prognosis for relapse, and only ERCC1 had an influence on the overall survival of TGCT patients treated with platinum-based chemotherapy. These may represent markers that predict poor clinical outcome and response to cisplatin.

ARTICLE INFO

Fernanda B. Morrone
http://orcid.org/0000-0002-2709-2801

Keywords:
transglutaminase 2 [Supplementary Concept]; Testicular Neoplasms; Cisplatin

Int Braz J Urol. 2020; 46: 353-62

Submitted for publication:
January 08, 2019

Accepted after revision:
September 17, 2019

Published as Ahead of Print:
October 30, 2019

INTRODUCTION

Testicular tumors account for 1% of all cancers in men. It is most frequent in men 15-35 years old and thus involves always a dramatic diagnosis (1). The very majority are testicular germ cell tumors (TGCT), where 50% are seminomas, 40% non-seminomas and the others are mixed tumors (1, 2). Even with the advent of new drugs in chemotherapy, cisplatin remains the treatment regimen with most curative potential for testicular cancer (3). Cisplatin cytotoxic activity results of interactions with DNA and the inability to repair DNA strand can lead to tumor cell apop-

tosis (3-5). In fact, adducts between platinum and DNA inhibit cellular processes, such as replication, transcription, translation and DNA repair (3). The decrease in cellular respiration can produce reactive oxygen species, resulting in lipid peroxidation (4). Furthermore, cisplatin binding to the mitochondrial DNA leads to decreased ATP and thus the decrease in ATPase activity and modification of the calcium content (4).

However, a group of testicular cancer patients may have a very unfavorable evolution and insensitivity to the main therapeutic agent chemotherapy (CT), cisplatin. Around 20-30% of the cases relapse and a second line of CT is necessary (4). Several mechanisms of cisplatin resistance have been proposed. Studies have linked the expression of excision repair cross-complementation group 1 (ERCC1) gene to chemoresistance as well as to poor survival in many types of cancer such as non--small-cell lung cancer, ovarian and gastric tumors (6-9). In TGCT cancer cell lines it has been reported an association of the cisplatin non-sensitivity with high levels of ERCC1, suggesting that this marker could be a potential mediator of response to cisplatin and a prognostic factor (10). Likewise, the overexpression of ERCC1 and XPF in TGCT was previously described during the progression of seminoma to non-seminoma (11). In addition, the transcription factor nuclear factor kappa-B (NF-κB) has been described to mediate cisplatin resistance. NF-κB is involved in many cellular functions, including the regulation of apoptosis and platinum--based chemotherapy resistance (12). Other studies demonstrate its role in tumorigenesis, CT resistance and a worse prognosis in bladder and head and neck cancer (12-14). Another marker is transglutaminase 2 (TG2), a trans-peptidase with a wide distribution in various tissues that plays an important role in malignancy progression by suppressing apoptosis (15). It is overexpressed in several neoplasms such as breast, ovaries, pancreas, and colon (16). TG2 is considered a prognostic marker in various cancers, due to its participation in promoting malignant cell mobility, invasion, metastasis, and chemoresistance, especially by platinum (17). Further mechanisms can be involved in platinum resistance such as decreased tumor blood flow, reduced platinum uptake, increased efflux, decreased binding, DNA repair, alteration of antiapoptotic factors and effects of various signaling pathways, among others (18).

A previous study showed that high expression of ERCC1 was associated with non-sensitivity to cisplatin-based CT in patients with non-seminomas TGCT (10), but little is known about other mechanisms involved in platinum resistance in testicular cancer. Therefore, the identification of other molecular markers to platinum-resistance is essential to a better treatment selection, avoiding unnecessary toxicity associated with platinum-based CT. In this study, we assessed the correlation of NF-κB, TG2 and ERCC1 expression with clinical outcomes in patients with TGCT treated with standard platinum combinations.

PATIENTS AND METHODS

Study design and data collection

A retrospective study was performed to evaluate tumor markers of cisplatin resistance in patients with testicular cancer receiving chemotherapy treatment. Eligible patients included male individuals (aged 18 years or above) with the confirmed diagnosis of testicular germ cell tumors. Seventy--six (76) cases of patients diagnosed with testicular cancer were evaluated in the Oncology Department--Hospital São Lucas/PUCRS in the period 2001 to 2011. Twenty-six 26 patients were excluded from the study due to the following reasons: lack of adherence to treatment or follow-up, incomplete data and loss of paraffin blocks. Histological indicative of TGCT was required to confirm the diagnosis. Data collection was retrospectively done through medical chart analysis of the cases treated. Patient's characteristics and tumor markers alpha-fetoprotein (AFP), beta-hCG and lactate dehydrogenase (LDH) were collected. The measurement of the tumor markers was made usually after the first-month post orchiectomy. The cut-off points and patient's stratification risk were evaluated according to the International Germ Cell Consensus Classification (IGCCCG) (19). This study was approved by the Institutional Ethics Committee of PUCRS (CEP number 0804398).

End-points

The endpoints were the relapse/recurrence rate and overall survival (OS). Recurrence was de-

fined when the progression of disease in computer tomography was confirmed. OS was calculated from the time of diagnosis to the date of death. The follow--up time for recurrence and OS was of 120 months for any cause of death.

Immunohistochemistry

To determine the expression of ERCC1, NF-κB and TG2 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, EUA), in the germ cell tumors we performed immunohistochemistry assay (9, 13, 20). The tumors were excised after surgery and fixed in buffered neutral formalin, sectioned, processed to paraffin wax and mounted onto a microscope slide. For the immunostaining study, sections were deparaffinized and rehydrated. The sections were submitted to antigenic retrieval being incubated with TRIS-EDTA, pH 9.0 for 30 minutes in a water bath at 98°C. For detection of the antibodies, it was used the REVEAL Biotin-Free Detection System (Spring Bioscience). The incubation of the primary antibodies (anti-NF-κB p65, clone C22B4, anti-TG2 clone CUB7402, anti-ERCC1, clone 8F1) was performed overnight at 4°C. Chromogenic detection (DAB) was used and the slides were counterstained with hematoxylin. The slides were mounted with glass coverslips using Canada Balsam and viewed with a microscope equipped with a camera. Images were captured in 400x amplification. For control experiments, primary antibody was omitted and evaluated for specificity or background staining levels. ERCC1, NF-kB and TG2 expression was considered as positive or negative by a pathologist blinded to the clinical outcome of each patient. The staining intensity was graded on a scale of 0 to 3. The percentage of positive nuclei was calculated for each specimen, and a proportion score was assigned (0 if 0%, 0.1 if 1 to 9%, 0.5 if 10 to 49% and 1.0 if 50% or more), as previously described (21). This proportion score was multiplied by the staining intensity of nuclei to obtain a final semi-quantitative H score. The median value of all the H scores was a priori chosen as a cut off point for separating positive tumors from negative tumors.

Statistical analysis

Quantitative data were described as mean±standard deviation (SD). Categorical data were presented by counts and percentages. Fisher's exact test or Pearson Chi-Square were used in categorical data. To obtain estimates of the association between ERCC1, NF-κB and TG2 markers with the occurrence of relapse we used a negative binomial regression model that provided relative risk estimates and their 95% confidence intervals. The relative risk was adjusted by age, stage, AFP, beta-hCG, and LDH histology. The differences in OS between categories of interest were analyzed using the log-rank test, and the hazard ratios (HRs) of the adjusted ERCC1, NF-κB and TG2 were calculated using the Cox model. The survival curves were constructed using the Kaplan-Meier method and significant between-group differences were assessed by the log-rank test. The significance level was set at α=0.05. Data were analyzed with the aid of the program SPSS version 22 and SigmaPlot version 11.

RESULTS

In this study, we assessed the correlation of NF-κB, TG2 and ERCC1 expression to clinical outcomes in 50 patients with TGCT treated with standard platinum combinations. The characteristics of the patients studied are presented in Table-1. Median age (range) of the group analyzed was 28.0 (18 to 45) years, 18 (36%) patients were clinical stage I, 10 (20%) were clinical stage II and 21 were stage III (42%), 12 cases (24%) were of seminoma and 38 cases (76%) of non-seminoma. Patient's stratification risk for non-seminoma was 16% poor prognosis, 38% intermediate risk and 46% good prognosis and, 58% good prognosis and, 42% intermediate to the seminoma cases.

The protocols of CT administered to the patients studied were in agreement with the currently first-line treatment pattern for TGCT (15). Patients received intravenously: BEP (cisplatin 20mg/m^2 on days 1 to 5, etoposide 100mg/m2 on days 1 to 5 and bleomycin 30UI, on days 2, 9 and 16) or EP (cisplatin 20mg/m^2, days 1 to 5 plus etoposide 100mg/m^2 days 1 to 5), every 21 days, intravenously (22). In this study, 36 (72%) patients received BEP (x3), 14 (28%) received EP (x4), and 4 (8%) patients used radiotherapy after CT (Table-1). The assessment of tumor markers

Table 1 - Characteristics of testicular cancer patients studied (n=50).

	n	(%)
Age (years)		
median	28.0	
range	18 to 45	
Clinical stage, no. (%)		
CS I	18	(36)
CS II	10	(20)
CS III	21	(42)
Histology, no. (%)		
Seminoma	12	(24)
Non-seminoma	38	(76)
Risk stratification, no. (%)		
Seminoma		
Good	7	(58)
Intermediate	5	(42)
Non-seminoma		
Good	18	(46)
Intermediate	14	(38)
Poor	6	(16)
Chemotherapy, no. (%)		
BEP (x3)	36	(72)
EP (x4)	14	(28)
Radiotherapy, no. (%)	4	(8)
Alpha-fetoprotein, no. (%)		
<1000ng/mL	16	(32)
≥1000ng/mL	34	(68)
Beta-hCG, no. (%)		
<1000ng/mL	15	(30)
≥1000ng/mL	35	(70)
LDH, no. (%)		
<1.5 x normal	22	(44)
≥1.5 x normal	28	(56)
Recurrence	22	(44)

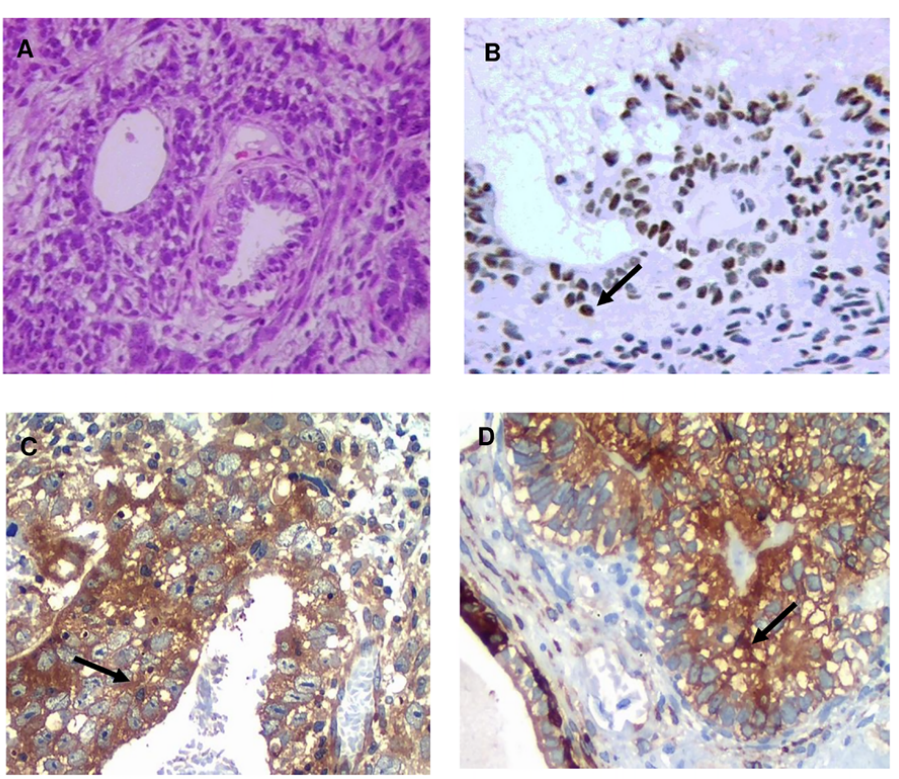
Date are presented as mean±standard deviation, median, and range of counts (percentage).
LDH = Lactate dehydrogenase; **BEP** = bleomycin, etoposide, and cisplatin; **EP** = etoposide and cisplatin; **CS** = clinical stage

was made after the orchiectomy. The AFP, beta--hCG, and LDH were elevated, on the 30h day post orchiectomy, in 68%, 70% and 56% of cases, respectively (Table-1). Immunodetection for ERCC1, NF-κB, and TG2 markers was positive in 42%, 76% and 46% of the patient's samples analyzed, respectively, and there were no statistically significant differences between seminoma and non--seminoma (Figures 1 A, B and C, Table-2).

The relative risk (RR) of ERCC1, NF-κB, and TG2 for testicular cancer relapse after completion of chemotherapy are depicted in Figure-2. It is presented also the adjusted RR for possible confounding factors in the outcome. The data on ERCC1 expression was significantly associated with a higher risk of relapse. When we adjusted stratified for factors such as age, clinical stage, alpha-fetoprotein, beta-hCG, lactate dehydrogenase, and histology non-seminoma, there was persistent the risk of recurrence (Figure-2A). Interestingly, we showed, for the first time, that the risk for relapse is around three times as high in the group NF-κB positive when compared to NF-κB negative, and this difference remains even after the adjustment of a potential factor of influence, with the exception of the tumor maker LDH (Figure-2B). No differences were observed with TG2 marker (Figure-2C). Interestingly, when we evaluated the impact of ERCC1 positive plus NF-kB positive versus ERCC1 positive plus NF-kB negative, there was a significant increase in the risk of recurrence for the markers combined positiveness (71.4% vs. 29.4%; p=0.001).

The evaluation of overall survival among patients with ERCC1-negative tumor, 1, 3, 5 and 10-year overall survival rate were 100%, 96%, 89% and 62%, compared to 100%, 85%, 57% and 9% for patients with positive expression of ERCC1 (p=0.001) (Figure-3A). The levels of NF-κB and TG2 protein expression had no significant influence on overall survival (Figures 3B and C).

Figure 1 - Representative images of H&E and immunostaining for the tumor markers (x400): A) H&E of non-seminoma testicular Tumor. Arrows indicate immunopositivity for: B) ERCC1; C) NF-κB; D) TG2.



(ERCC1, Excision repair cross-complementation group; NF-κB, factor nuclear kappa B; TG2, transglutaminase 2; H&E, hematoxylin, and eosin).

Figure 2 - A) Relative risk for relapse to ERCC1 positive cases; stratified mode adjustments for factors such as age, clinical stage (CS), alpha-fetoprotein (AFP), beta-hCG, lactate dehydrogenase (LDH) and histology non-seminoma. B) The relative risk for relapse to NF-κB positive cases; stratified mode adjustments for factors such as age, clinical stage (CS), alpha-fetoprotein (AFP), beta-hCG, lactate dehydrogenase (LDH) and histology non-seminoma. C) The relative risk for relapse to TG2 positive cases; stratified mode adjustments for factors such as age, clinical stage (CS), alpha-fetoprotein (AFP), beta-hCG, lactate dehydrogenase (LDH) and histology non-seminoma. Amounts right corresponds to p and ranges (n=50).

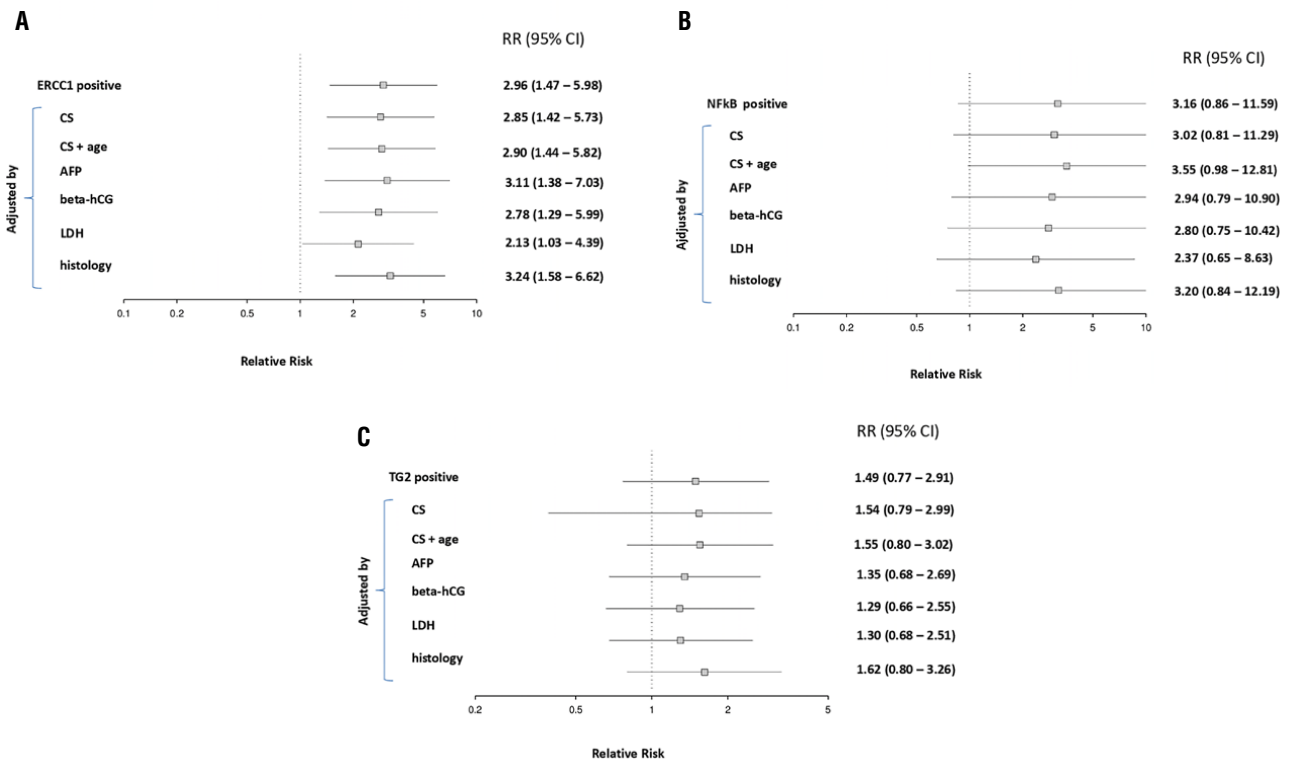


Table 2 - Immunohistochemical analysis of ERCC1, NF-κB, and TG2 in patients with testicular cancer (n=50).

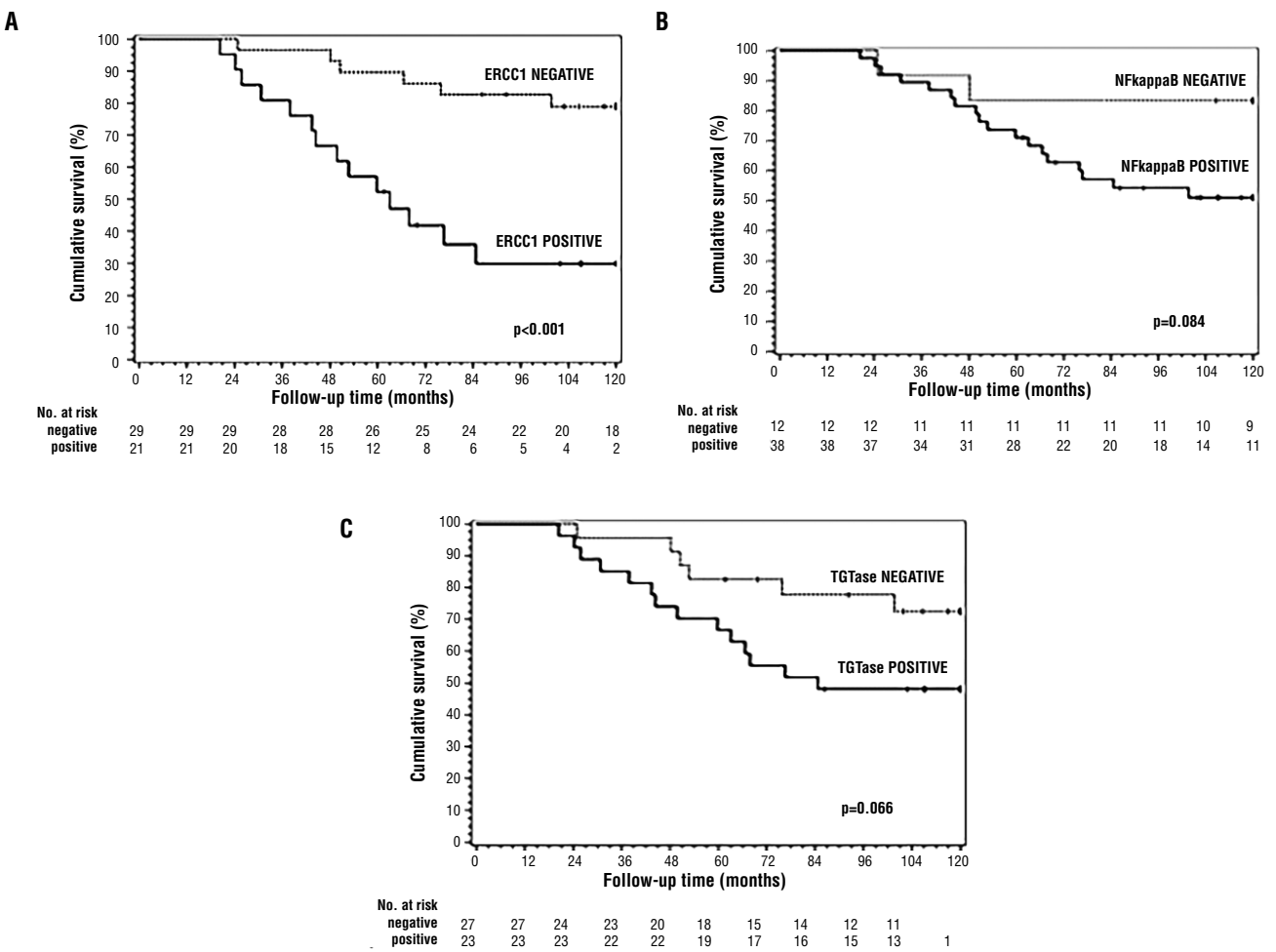
Marker positive	Total no. (%)	Seminoma no. (%)	Non-seminoma no. (%)	P value
ERCC1	21 (42.0)	3 (14.3)	18 (85.7)	0.171
NF-κB	38 (76.0)	8 (21.1)	30 (78.9)	0.385
TG2	23 (46.0)	8 (34.8)	15 (65.2)	0.094

ERCC1 = Excision repair cross-complementation group; **NF-κB** = nuclear factor kappa B; **TG2** = transglutaminase 2.

DISCUSSION

Platinum-based chemotherapy remains the first line of treatment of TGCT for more than 30 years (1). This study aimed to assess new molecular markers involved in cisplatin resistance, and their correlation with tumors relapse in patients with testicular tumors. In this study, the majority of patients studied were young males with TGCT non-seminoma and had a poor or intermediate prognosis classification. One of the main problems related to the recurrence of TGCT is platinum resistance and the mechanisms associated with cisplatin resistance involve many different cellular

Figure 3 - Kaplan-Meier estimate of overall survival probability according to ERCC1, p <0.001. A) NF-κB, p=0.084; B) and TG2, p=0.066; C). The differences in OS between categories of interest were analyzed using the log-rank test, and the significance level was set at α=0.05.



processes (18, 23). Previous studies have demonstrated that platinum damage can be repaired by the nucleotide excision repair system, especially by ERCC1 (21). Our results showed that the expression of ERCC1 is associated with increased risk for TGCT relapse after treatment with platinum-based chemotherapy. When multivariate analysis was performed, none of the confounding factors in the outcome was able to change this point. These results show, in an important manner, that ERCC1 overexpression may predict that the curative chemotherapy has a relative risk of 2.96 to failure. In effect, predictive and prognostic values of ERCC1 expression have been studied in many solid tumors. It has been reported in some studies in ovarian, head and neck, and particularly in lung cancer that this marker could predict the response to chemotherapy (7, 9, 10, 24, 25). Corroborating to our results, Mendoza et al. (10) demonstrated that high levels of ERCC1 were associated with non-cisplatin sensitivity, suggesting that ERCC1 could be used as a potential indicator of the response to cisplatin and prognosis in non-sensitive TGCTs. Furthermore, the study of Olaussen et al. (9) demonstrated that the benefit of adjuvant chemotherapy with cisplatin was lost when there was a

high expression of ERCC1 in the small-cell lung cancer tumor. In patients with squamous cell carcinoma, the expression of ERCC1 predicts a lower response to chemotherapy treatment (25). Interestingly, overexpression of ERCC1 gene seems to be associated with a reduction in the therapeutic efficacy of cisplatin, and the clinical response varies with polymorphisms ERCC1 (6). The mechanism by which ERCC1 contributes to cisplatin resistance involves a nucleoside excision repair, which removes platinum-DNA adducts and repairs the DNA double-strand breaks, and other reports mention an inherent biologic characteristic of the tumor (24, 25). Our results suggest that the evaluation of ERCC1 expression may contribute as a more accurate predictor of patient's selection who are at increased risk of recurrence following standard treatment with cisplatin.

The data presented herein showed, for the first time, the expression of NF-κB in TGCT. The detection of high levels of NF-κB in patients with testicular cancer supports the hypothesis of a higher risk of recurrence after the treatment with cisplatin. Although there were no differences in the risk of recurrence for positive expression of NF-κB alone, we observed a significant increase in the risk of recurrence when we evaluated combined positive expression of ERCC1 plus NF-κB. The mechanism of resistance could be explained since cisplatin significantly increases NF-κB DNA binding activity, and NF-κB may antagonize apoptosis induced by cisplatin (26, 27). It has been described that NF-κB inhibitors augment platinum activity against some cancer cell lines and tumor xenograft models (28, 29). On the other hand, NF-κB activation increased cisplatin efficacy in some cell lines, and enhanced efficacy of higher cisplatin concentrations (30). For the other marker studied, there was no significant association between TG2 with the recurrence of TGCT.

It is worth to mention that due to its retrospective design, the number of clinical samples, and survival bias could potentially threaten the conclusions of this study. A further prospective cohort of patients should be performed in order to confirm the results achieved herein. Another limitation of this study is the inherent weaknesses of immunohistochemical staining, such as its semi-quantitative nature and interobserver variation. It is worth to consider that in this study the markers were analyzed only after surgery, which could limit the assessment.

In conclusion, we demonstrated that ERCC1 and NF-κB expression confer a worse prognosis for recurrence in patients with TGCT treated with standard platinum-based chemotherapy. The identification of resistance markers in TCGT patients who are potentially non-sensitive to cisplatin chemotherapy can improve their quality of life by avoiding the adverse effects caused by this agent.

ACKNOWLEDGMENTS

This work was supported by CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) scholarships and CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior--Brasil) - Finance Code 001, PUCRS (Pontifícia Universidade Católica do Rio Grande do Sul). The authors thank Dr. Wagner M, for his technical advice with the statistical analysis, Dr. Gaiger AM for immunohistochemical analysis, and Bittencourt B for the help in data collection.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Feldman DR, Bosl GJ, Sheinfeld J, Motzer RJ. Medical treatment of advanced testicular cancer. JAMA. 2008;299:672-84.
2. Goldberg H, Klaassen Z, Chandrasekar T, Fleshner N, Hamilton RJ, Jewett MAS. Germ Cell Testicular Tumors-Contemporary Diagnosis, Staging and Management of Localized and Advanced disease. Urology. 2019;125:8-19.
3. Vasey PA. Resistance to chemotherapy in advanced ovarian cancer: mechanisms and current strategies. Br J Cancer. 2003;89(Suppl 3):S23-8.
4. Martin LP, Hamilton TC, Schilder RJ. Platinum resistance: the role of DNA repair pathways. Clin Cancer Res. 2008;14:1291-5.

5. Chovanec M, Abu Zaid M, Hanna N, El-Kouri N, Einhorn LH, Albany C. Long-term toxicity of cisplatin in germ-cell tumor survivors. Ann Oncol. 2017;28:2670-9.
6. Kang CH, Jang BG, Kim DW, Chung DH, Kim YT, Jheon S, et al. Differences in the expression profiles of excision repair crosscomplementation group 1, x-ray repair crosscomplementation group 1, and betaIII-tubulin between primary non-small cell lung cancer and metastatic lymph nodes and the significance in mid-term survival. J Thorac Oncol. 2009;4:1307-12.
7. Friboulet L, Olaussen KA, Pignon JP, Shepherd FA, Tsao MS, Graziano S, et al. ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. N Engl J Med. 2013;368:1101-10.
8. Urun Y, Leow JJ, Fay AP, Albiges L, Choueiri TK, Bellmunt J. ERCC1 as a prognostic factor for survival in patients with advanced urothelial cancer treated with platinum based chemotherapy: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017;120:120-6.
9. Olaussen KA, Dunant A, Fouret P, Brambilla E, André F, Haddad V, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med. 2006;355:983-91.
10. Mendoza J, Martínez J, Hernández C, Pérez-Montiel D, Castro C, Fabián-Morales E, et al. Association between ERCC1 and XPA expression and polymorphisms and the response to cisplatin in testicular germ cell tumours. Br J Cancer. 2013;109:68-75.
11. Köberle B, Brenner W, Albers A, Usanova S, Thüroff JW, Kaina B. ERCC1 and XPF expression in human testicular germ cell tumors. Oncol Rep. 2010;23:223-7.
12. Koga F, Yoshida S, Tatokoro M, Kawakami S, Fujii Y, Kumagai J, et al. ErbB2 and NFκB overexpression as predictors of chemoradiation resistance and putative targets to overcome resistance in muscle-invasive bladder cancer. PLoS One. 2011;6:e27616.
13. Li Z, Yang Z, Lapidus RG, Liu X, Cullen KJ, Dan HC. IKK phosphorylation of NF-κB at serine 536 contributes to acquired cisplatin resistance in head and neck squamous cell cancer. Am J Cancer Res. 2015;5:3098-110.
14. Taniguchi K, Karin M. NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol. 2018;18:309-24.
15. Tabolacci C, De Martino A, Mischiati C, Feriotto G, Beninati S. The Role of Tissue Transglutaminase in Cancer Cell Initiation, Survival and Progression. Med Sci (Basel). 2019;7.
16. Huang L, Xu AM, Liu W. Transglutaminase 2 in cancer. Am J Cancer Res. 2015;5:2756-76.
17. Cao L, Petrusca DN, Satpathy M, Nakshatri H, Petrache I, Matei D. Tissue transglutaminase protects epithelial ovarian cancer cells from cisplatin-induced apoptosis by promoting cell survival signaling. Carcinogenesis. 2008;29:1893-900.
18. Stewart DJ. Mechanisms of resistance to cisplatin and carboplatin. Crit Rev Oncol Hematol. 2007;63:12-31.
19. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol. 1997;15:594-603.
20. Park MJ, Baek HW, Rhee YY, Lee C, Park JW, Kim HW, et al. Transglutaminase 2 expression and its prognostic significance in clear cell renal cell carcinoma. J Pathol Transl Med. 2015;49:37-43.
21. Reed E. Platinum-DNA adduct, nucleotide excision repair and platinum based anti-cancer chemotherapy. Cancer Treat Rev. 1998;24:331-44.
22. Culine S, Kerbrat P, Kramar A, Théodore C, Chevreau C, Geoffrois L, et al. Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol. 2007;18:917-24.
23. Sonnenburg D, Spinella MJ, Albany C. Epigenetic Targeting of Platinum Resistant Testicular Cancer. Curr Cancer Drug Targets. 2016;16:789-95.
24. Polat G, Yılmaz U, Anar C, Kömürcüoğlu B, Aydoğdu Z. Is there relationship between excision repair cross-complementation 1 expression level and response to treatment and prognosis in an advanced stage lung cancer treated with cisplatin-based chemotherapy? Indian J Cancer. 2015;52:277-80.
25. Jun HJ, Ahn MJ, Kim HS, Yi SY, Han J, Lee SK, et al. ERCC1 expression as a predictive marker of squamous cell carcinoma of the head and neck treated with cisplatin-based concurrent chemoradiation. Br J Cancer. 2008;99:167-72.
26. Kim JK, Kim KD, Lee E, Lim JS, Cho HJ, Yoon HK, et al. Up-regulation of Bfl-1/A1 via NF-kappaB activation in cisplatin-resistant human bladder cancer cell line. Cancer Lett. 2004;212:61-70.
27. Eichholtz-Wirth H, Sagan D. IkappaB/NF-kappaB mediated cisplatin resistance in HeLa cells after low-dose gamma-irradiation is associated with altered SODD expression. Apoptosis. 2000;5:255-63.
28. Upadhyay AK, Singh S, Chhipa RR, Vijayakumar MV, Ajay AK, Bhat MK. Methyl-beta-cyclodextrin enhances the susceptibility of human breast cancer cells to carboplatin and 5-fluorouracil: involvement of Akt, NF-kappaB and Bcl-2. Toxicol Appl Pharmacol. 2006;216:177-85.

29. Mohammad RM, Banerjee S, Li Y, Aboukameel A, Kucuk O, Sarkar FH. Cisplatin-induced antitumor activity is potentiated by the soy isoflavone genistein in BxPC-3 pancreatic tumor xenografts. Cancer. 2006;106:1260-8.

30. Shehata M, Shehata M, Shehata F, Pater A. Apoptosis effects of Xrel3 c-Rel/Nuclear Factor-kappa B homolog in human cervical cancer cells. Cell Biol Int. 2005;29:429-40.

Correspondence address:
Fernanda B. Morrone, MD
Laboratório de Farmacologia Aplicada,
Escola de Ciências da Saúde, Pontifícia Universidade
Católica do Rio Grande do Sul - PUCRS,
Porto Alegre, RS, Brasil
Av. Ipiranga, nº 6681, Predio 12 C
Porto Alegre, Brasil
Cep: 90619-900
E-mail: fbmorrone@gmail.com

ORIGINAL ARTICLE

Vol. 46 (3): 363-373, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0023

Special emphasis on bone health management in prostate cancer patients: a prospective longitudinal study

Ashish Sharma [1], Rahul Janak Sinha [1], Gaurav Garg [1], Samarth Agarwal [1], Asif Akhtar Statistician[1], Vishwajeet Singh [1]

[1] *King George's Medical University, Lucknow, India*

ABSTRACT

Introduction: Use of androgen deprivation therapy (ADT) in carcinoma prostate (CaP) has deleterious effect on bone mineral density (BMD) leading to increase incidence of osteoporosis and skeletal-related events. We evaluated bone health status and impact of bone-directed therapy (BDT) and ADT on BMD in these patients from Jan 2015-Dec 2018.

Materials and Method: Baseline bone health was assessed using Tc-99 MDP Bone scan/ DEXA scan for patients on ADT. Monthly zoledronic acid (ZA) was given to high-risk candidates (T-score ≤2.5 or previous hip/vertebral fracture) or Skel et al. metastatic patients who were receiving ADT. Baseline and follow-up (at 12-months) BMD using DEXA scan at various sites (spine, femur total, femur neck and radius) and subjective improvement in bony pain using Numeric Pain Rating Score after administration of ZA were compared.

Results: A total of 96-patients of locally advanced and metastatic prostate cancer receiving ADT with or without BDT were included in the study cohort. Mean age of presentation was 68.4±15.61 years. Median serum PSA was 32.2±13.1ng/mL. There was significant improvement in mean BMD (T-score) in 64-patients post ZA therapy at 12-months (at femoral total, femoral neck and spine; 0.95, 0.79 and 0.68, respectively) ($p < 0.05$) while there was significant deterioration in mean BMD at 12-months (at spine, femoral neck and femoral total; -0.77, -0.55 and -0.66, respectively) in 32 patients who did not receive ZA and were on ADT ($p < 0.05$). Pain scores significantly decreased in patients after 12-months of ZA use (-2.92±2.16, $p < 0.01$).

Conclusion: Bone-directed therapy (Zoledronic acid) leads to both subjective and objective improvement in bone health of prostate cancer patients on ADT.

ARTICLE INFO

Ashish Sharma
http://orcid.org/0000-0002-6337-8401

Keywords:
Prostatic Neoplasms; Longitudinal Studies; Population Health Management

Int Braz J Urol. 2020; 46: 363-73

Submitted for publication:
January 09, 2019

Accepted after revision:
September 15, 2019

Published as Ahead of Print:
October 30, 2019

INTRODUCTION

Carcinoma of the prostate (CaP) has the highest incidence of Skel et al. metastases among all urological malignancies. Skel.et al. metastasis in these patients causes some of the most worrisome symptoms, which includes intractable bony pain, pathological fracture, spinal cord compression and paresis (1). Prostate cancer usually occurs in elderly population in which the prevalence of osteoporosis is already common and further use of androgen deprivation therapy (ADT) as a treatment modality in these patients has cumulative deleterious effect on bone mineral density (BMD)

leading to increase in osteoporosis and skeletal fracture risk. Development of osteoporosis in these patients appears to increase steadily with duration of ADT with an annual bone loss of 0.6-9.6% and most significant loss occurs within the first year of initiation of ADT. Thus, maintaining the optimal bone health status should be on priority while managing these patients. Unfortunately, this aspect of prostate cancer often remains neglected and there is widespread ignorance amongst medical community about optimum management of bone health in these patients even today (2, 3). Failure to properly screen these patients is detrimental to both quantity and quality of life, given the consistent increase in the life expectancy of CaP patients. The present study was undertaken to study the bone health with special emphasis in prostate cancer patients so that early intervention could be attempted to prevent skeletal related events and thus improve their quality of life.

OBJECTIVES

To evaluate clinical profile (like demographical characteristics, presenting clinical symptoms, baseline serum prostate specific antigen level, vitamin-D deficiency, Gleason grading, presence and pattern of bony involvement) in patients with prostate cancer who presented to tertiary care institute of a developing nation.

To evaluate the bone health with DEXA scan & bone scan and to assess the impact of bone-directed therapy (BDT) in improving bone health in these patients.

To reduce skeletal-related events in prostate cancer patients by early intervention thus reducing morbidity and mortality.

MATERIAL AND METHODS

We recruited consecutive patients of CaP of all age group who presented to the department of Urology at a tertiary care hospital of North India from January 2015 to December 2018. Patients with metabolic or congenital bone disease, prostate secondaries, other active malignancy, central nervous disorders, and moribund status were excluded from the study. Institutional review board clearance and written informed consent from all patients was obtained. This time bound prospective study was registered with Central Trial Registry of India (CTRI) with reference number CTRI/2016/08/007205 (5). Workup and management of CaP patients of study cohort was done as per the European Association of Urology (EAU) guidelines and patient's personal preference (4). Patients were followed every 3 months with serum prostate specific antigen (PSA) levels to look for adequacy of cancer control. Castrate resistant prostate cancer patients were started on the appropriate chemotherapy (docetaxel)/abiraterone/enzulatamide therapy or watchful waiting according to the EAU guidelines and patient preferences.

Baseline bone health was assessed using Tc-99 MDP Bone scan (presence of bony pain, Gleason score >7, serum PSA >10ng/mL and palpable disease cT2/T3) and Dual Energy X-ray Absorptiometry (DEXA) scan for patients on ADT for at least 6-months duration, or presence of clinical risk factors like past history of fracture, excessive alcohol consumption, current smoking and vitamin D deficiency. The BMD was measured by T-score at spine, total femur, femur neck and radius bone in gm/cm^2. Advanced prostate cancer patients (locally advanced and metastatic) who were on ADT and in whom DEXA scan was indicated and could be obtained, served the final study cohort. Bone-directed therapy (injection of Zoledronic Acid 4mg intravenous infusion monthly+Vitamin D+Calcium Supplementation) was started in these patients of androgen deprivation therapy (ADT) with either positive bone scan or with high fracture risk on DEXA scan (T score $\leq$2.5) or positive history of previous hip/vertebral fracture. Dose modifications of zoledronic acid (ZA) therapy was done based on renal function status (creatinine clearance>60mL/min: 4mg, 60-40mL/min: 3.5mg, 40-30mL/min: 3mg and if <30mL/min then contraindicated). The baseline and follow-up (at 12-months) BMD at various sites were compared pre and post ZA at spine, femur total, femur neck and radius using DEXA scan. Subjective measurement of pain was done using 11-points Numeric Pain Rating Score (NRS) where 0 indicates no pain, 1-3 indicates mild pain, 4-6

indicates moderate pain and >7-10 means severe pain in patients who received ZA at baseline and after 12-months (6). Bone-directed therapy (injection of Zoledronic Acid 4mg+Vitamin D+Calcium Supplementation) was administered on monthly basis. DEXA scan was repeated after 12 months to look for changes in bone health.

Statistical analysis

Statistical analysis was performed by an independent statistician using IBM SPSS Statistics ver. 21.0 software (IBM Co., Armonk, NY, USA). T score (BMD) at baseline and after 12 months of therapy was compared at spine, femur neck, total femur and wrist using Wilcoxon Signed Ranks Test. Subjective relief in pain was analyzed by the patient's perception of pain pre and post injection of Zoledronic Acid therapy on an 11-points numeric pain rating scale and compared using the Wilcoxon Signed Ranks test. Bone health of patients who were on ADT but did not receive injection of Zoledronic Acid therapy because of non-compliance, chronic kidney disease or financial constraint were compared with those who were on ADT with Zoledronic Acid (4mg monthly) administration, using the Mann-Whitney test. P value <0.05 was considered statistically significant.

RESULTS

We initially enrolled a total of 160 diagnosed prostate cancer patients of all stages. Out of these 160 patients, 135-patients (either locally advanced or metastatic stage) received ADT. Bone scan was obtained in 130 of these patients and it was positive in 100 patients. Ninety six patients with advanced prostate cancer (who were on ADT and in whom DEXA scan was indicated and could be obtained) were included in final study analysis as study subjects. Bone health could not be assessed in other patients due to non-availability of DEXA scan (either not indicated or could not be obtained due to non-compliance or financial reasons or lost to follow-up) and therefore, these patients were excluded from study. This study flow is depicted in Figure-1. Mean age of presentation was 68.4±15.61 years. Median serum PSA was 32.2±13.1ng/mL. Majority of these patients had osteopenia (29.2%) or osteoporosis (64.6%) on DEXA scan. Baseline clinical profile, radiological, pathological and therapeutic characteristics of these patients is depicted in Tables 1 and 2. Zoledronic acid therapy was initiated in 64 of our patients and were followed up with DEXA scan and subjective assessment of bony pain using Numeric Pain Rating Score at 12 months. These were termed as therapy (Bone-directed therapy) group. However, 32 patients were on ADT but did not received Zoledronic Acid therapy due to non-compliance, chronic renal insufficiency status, hypersensivity reactions and financial constraint. These patients served as control or non-therapy group in our study.

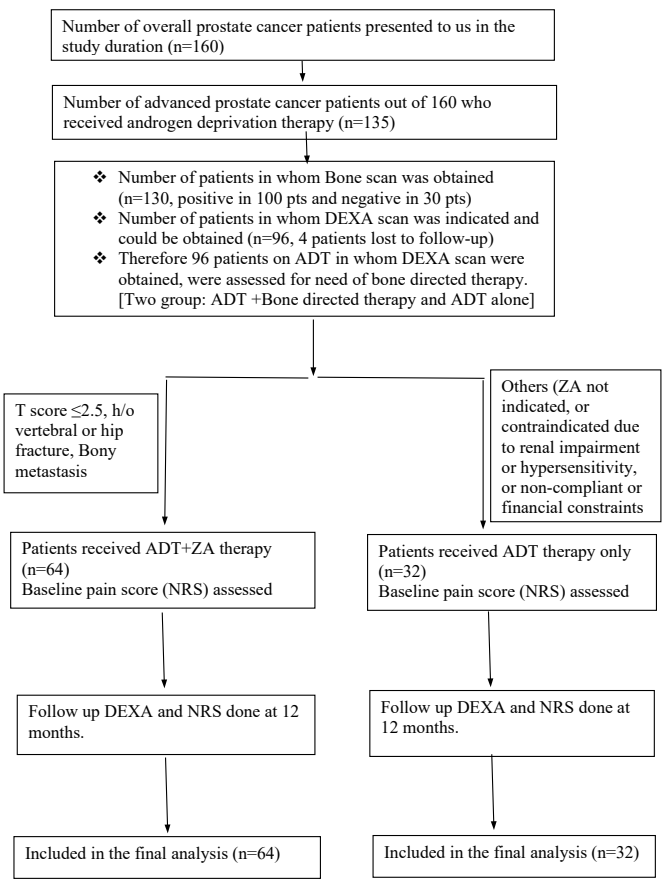
BMD measured as T-Score at various sites was found to improve statistically at all sites (at spine, femur total and femur neck) except radius in patients taking ZA therapy (64 patients) after 12-months (P <0.05) (Table-3, Figure-2). Most significant improvement in mean BMD after instituting Zoledronic acid therapy was noted in femoral total followed by femoral neck and spine (0.95, 0.79 and 0.68, respectively).

However, BMD changes after 12 months in patients on ADT and not receiving ZA therapy (32 patients) showed significant decrease in T score at all sites except radius (P <0.05) (Figure-3). Most significant deterioration in mean BMD in this group of patients was noted in spine followed by femoral neck and femoral total (-0.77, -0.55 and -0.66, respectively) (Table-3, Figure-4).

Pain scores significantly decreased in patients after 12-months of ZA use (-2.92±2.16, p <0.01) (Table-3, Figure-5). Pain Scores in patient on ADT not receiving the ZA therapy showed a significant deterioration at follow-up from a baseline of 2.81±1.32 to 4.41±2.54 at mean with a change of +1.60±1.88 (p=0.002).

Skeletal related events (spinal cord compression, need for radiotherapy or surgery for bony metastasis) were seen in 30 out of 160 (18.7%) enrolled patients during the four years of the study duration. Fracture rates were significantly lower in bone-directed therapy group (5.5%) as compared to non-therapy group (12.8%). (Relative risk: 0.29, 95% confidence interval: 0.28-0.41). Multi-

Figure 1 - Flow Chart of the study.



variate analysis (using Cox proportional hazards regression model) results showed that advanced age >70 years (HR-1.89, p=004), Gleason score ≥7 (HR-1.52, p=0.013), presence of bony pain (HR-2.80, p <001), presence of extra-spinal skeletal metastasis (HR-1.96, p=0.036) and absence of bone-directed therapy (HR-2.6, p=0.002) were associated with the risk of skeletal related events in prostate cancer patients. Twenty-four (25.0%) patients of study cohort died within the follow-up period of 4 years.

Zoledronic acid treatment was well tolerated by most of our subjects except 5 patients who developed mild fever and 4 patients who developed reversible multiple joint pain with fever which lasted for 1-2 days. These patients were treated with oral Paracetamol and recovered well. They did not discontinue the therapy. None of the patients developed osteonecrosis of the jaw in the current study. Zoledronic Acid not only prevents bone mineral density loss but also improves BMD, thus decreasing the fracture risk and diminishing the patient's perception of pain.

DISCUSSION

The present study from India is a sobering reminder of prostate cancer presentation in absence of PSA screening: Of all 160 patients, 63% had PSA >100ng/mL, approximately 92% patients with PSA >20ng/mL, 50% patients had Gleason 9, 93% patients had Gleason 7 or higher with much higher frequency of metastatic disease and use of bilateral orchiectomy as ADT modality. This study demonstrates that ZA therapy improved BMD and resulted in less pain and fewer skeletal events. It

Table 1 - Demographical data and baseline characteristics of prostate cancer patients (n=96).

Baseline Characteristic (N=96)	Number of Patients (N)	Percentage %
Age Distribution		
41-50	9	9.37
51-60	13	13.54
61-70	54	56.25
71-80	17	17.70
>80	3	3.12
Geographical Distribution		
Rural	37	38.54
Urban	59	61.45
ECOG Score		
PS 0	72	75.0%
PS 1	16	16.67%
PS 2	5	5.2%
PS 3	2	2.0%
PS 4	1	1.04%
Presenting Symptoms		
Voiding LUTS	50	52.08
Bony pain	29	30.20
Acute urinary obstruction	9	9.37
Hematuria	2	2.08
Incidental	6	6.25
Prostate Size (cc)		
20-40	35	36.45
41-60	27	28.12
61-80	20	20.83
81-100	10	10.41
>100	4	4.16
Serum PSA		
<4.0	2	2.08
4-20	5	5.20
20-100	27	28.12
>100	62	64.58
Baseline Serum Vit D (ng/mL)		
Deficiency (<10)	9	9.37%
Insufficiency (10-30)	69	71.87%
Sufficiency (30-100)	18	18.75%
Baseline Characteristics	Average ± SD	Range
BMI (kg/m^2)	22.5±3.34	15-32
Serum PSA (ng/dL)	32.2±13.1	0.02-2698
Mean ADT Duration (Months)	24.6±13.3	1-147
Mean Follow-Up Duration (Months)	32.8±12.2	8-48
Mean Duration of BDT (Months)	14.6 ±9.6	8-25

Table 2 - Description of radiological, pathological and therapeutic parameters.

Parameters	Number of Patients (N)	Percentage%
Biopsy (N=96)		
5+4	34	35.41
4+5	14	14.58
4+4	16	16.67
4+3	13	13.54
3+4	12	12.5
3+3	7	7.29
Gleason Grading (N=96)		
High Grade (>7)	62	64.58
low Grade (<=7)	34	35.33
Baseline DEXA Scan (N=96)		
Normal (T Score < -1.0)	6	6.25
Osteopenia (T Score -1.0 to -2.5)	28	29.17
Osteoporosis (T Score < -2.5)	62	64.58
Staging (N=96)		
Locally-advanced CaP	04	25.0%
Metastatic (Skeletal+Visceral)	92 (90+2)	75.0%
Pattern of Bony involvement (N=90)#		
Spine	84	93.33
Pelvis	72	80.0
Femur	40	44.44
Shoulder	27	30.0
Ribs	45	50.0
Skull	19	21.11
Sternum	10	11.11
Clavicle	3	3.33
Treatment Modality [single/multimodal]*		
Bilateral Orchidectomy	65	67.7
LHRH Agonists	8	8.33
LHRH Antagonists	2	2.08
Radical Prostatectomy+ADT/RT	2	2.08
Watchful waiting	3	3.12
Docetaxel Chemotherapy	2	2.08
Abiraterone therapy	5	5.20
Enzalutamide	3	3.12

Total no. exceeds 100% (n=90) as some patients have >1 bone involvement; * = Total no. exceeds 100% (n=96) as some patients received more than one treatment modality along study duration

Table 3 - Comparison of baseline and follow up BMD at various bone sites and Pain Scores with different therapeutic modalities.

BMD (T Score)	Baseline (Mean±SD)	Follow-Up (Mean±SD)	Difference (Mean±SD)	Z Score	P Value
Impact of ADT on BMD in patients receiving Bone-directed therapy (Zoledronic acid) at various bone sites (N=64)					
Spine	-0.91±1.62	0.59±2.10	0.68±1.12	-3.45	0.001*
Femur Neck	-1.90±1.43	-1.11±1.64	0.79±0.97	-2.89	0.002*
Femur total	-1.30±1.53	-0.55±1.02	0.95±0.91	-3.91	0.000*
Radius	-1.18±1.01	-1.24±1.32	0.06±0.77	-1.12	0.361
Impact of ADT on BMD in patients without Bone-directed therapy (Zoledronic acid) at various bone sites (N=32)					
Spine	-1.03±1.17	-1.80 ±1.50	-0.77±0.99	-2.62	0.012*
Femur Neck	-2.04±1.23	-2.70± 1.63	-0.65±0.75	-2.50	0.015*
Femur Total	-1.63±1.21	-2.18±1.57	-0.55±0.65	-2.63	0.005*
Radius	-1.06±1.43	-1.21±1.55	-0.15±0.17	-1.14	0.154
Impact of Zoledronic acid therapy on Bony Pain measured by Numeric Pain Rating Score (NRS) on 0-10 Scale (N=96)					
ZA Therapy Group (N=64)	5.11±1.80	2.19±1.34	-2.92±2.11	-3.53	0.0001*
Non-therapy Group (N=32)	2.81±1.30	4.41±2.45	+1.60±1.72	-2.26	0.020*

* P value<0.05

Figure 2 - Baseline and post-therapy (Zoledronic acid therapy) BMD (T-Score) showing improvement at all site except radius.

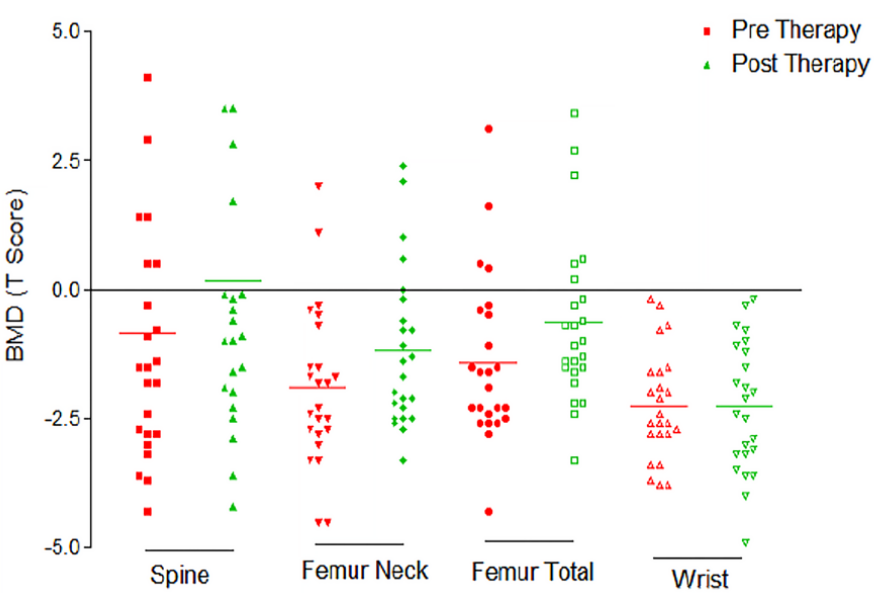


Figure 3 - Baseline and Follow-up BMD (T-Score) in patients on ADT without Zoledronic acid therapy showing worsening at all site except radius.

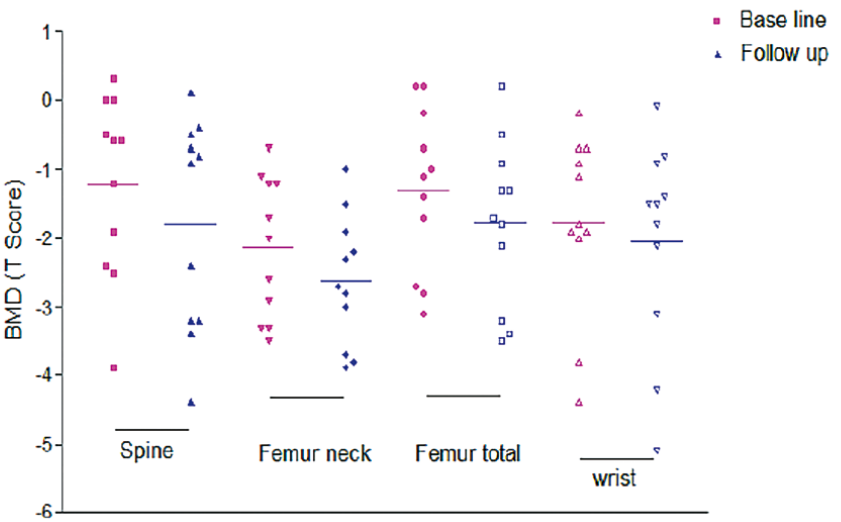
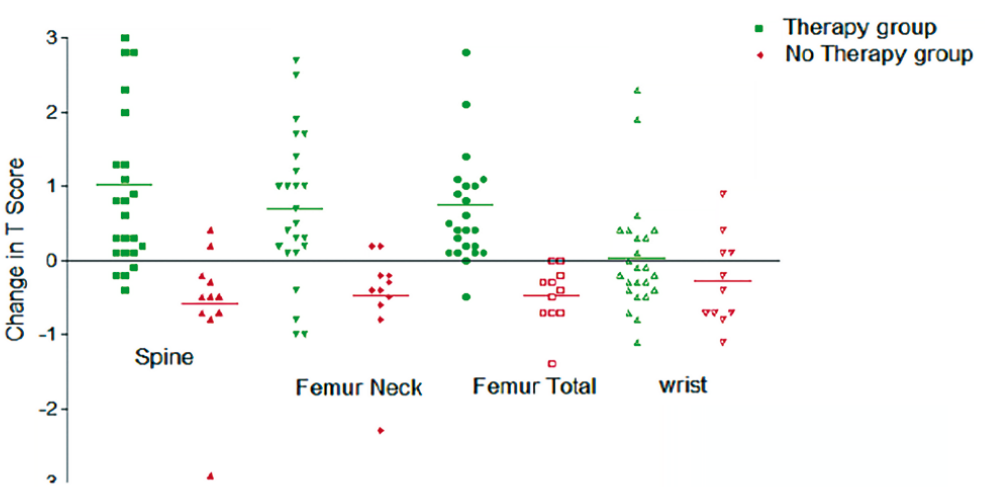


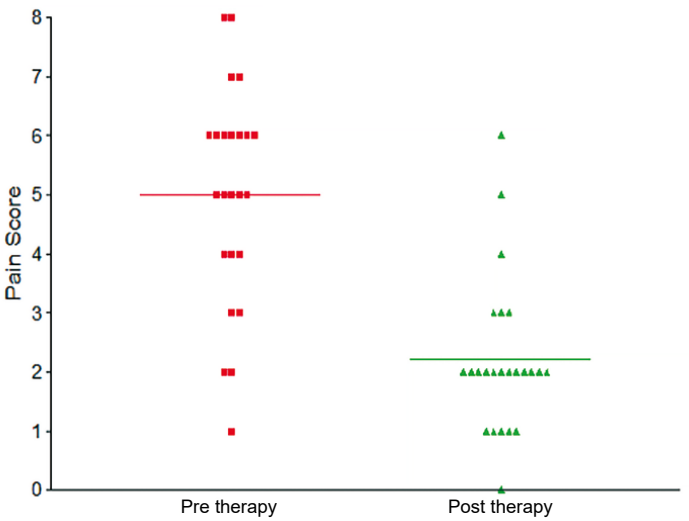
Figure 4 - Comparison of T-Scores in patients who received therapy and did not received therapy showing favourable results for therapy group.



also highlights that ADT associated bone loss is underreported and relatively neglected even in the present era.

The largest percentage (48.12%) of our total 160 patient cohort were between 60-70 years age group followed by 21.88% patients between 70-80 years group hence making it around 75% population greater than 60 years with average age being 68.4 years. This is in concordance with literature which stats that more than three quarter of cancer prostate occur after the age of 65 years (7), somewhat lower than median age of 72 years in another series (8). We had no patient under 40 years of age and only 10.6% were under 50 years suggesting that it is quite uncommon below the age of 50 years. The average age of death from carcinoma prostate is 77 years and has remained stable over the last three decades (9). Similarly in

Figure 5 - Comparison of pain scores pre and post Zoledronic acid therapy in patients on ADT showing a significant improvement in pain scores.



our series, we saw few patients (4.37%) in the age group above 80 years. It can also be explained by the fact that average life expectancy in India as per World Health Organisation, 2015, is around 66.9 years for men, thus, not many patients live long enough to present with the disease after 80 years of age.

The positive DRE finding in almost all our cases represent the late stage of presentation of the disease in this part of the world. In western countries, after the introduction of PSA testing, 81% of newly diagnosed men have localized disease, whereas the incidence of metastatic disease has decreased by 75% (10). Non-palpable cancers (AJCC clinical stage T1c) now account for 60-75% of newly diagnosed cancers (11). This is in contrast to the findings seen in our patients. By the time the patients present to us, they already have hard prostate and the diagnosis in almost all cases can be easily reached by simple digital rectal examination. As previously mentioned, around 20% patients come to us with bony pain as their first presenting symptoms, signifying lack of screening programme for cancer prostate in our country.

Incidence of bony metastases in prostate cancer patients is quite high in India. Majority (68.7%) of our study subjects (110 out of 160) were metastatic (on either bone scan/MRI/CECT scan) at presentation, while in western population about 80% of patients have localized disease at presentation (10). It shows that most of our patients have higher stage and grade at presentation and hence indicates poor prognosis, high morbidity and mortality at the time of diagnosis itself (Table-2). The most common site of metastases observed in our study was the spine in 93% cases followed by pelvis in 80% cases.

ADT is commonly used in our setting because most of the patients present in advance stage and are not the candidates for radical prostatectomy. Most common treatment modality used in our setting was bilateral orchidectomy followed by GnRH agonists. Most of the study subjects were from poor socioeconomic background and could not afford costly treatment of GnRH agonist and antagonist and hence chose bilateral orchidectomy. Androgen deprivation associated bone loss is an increasingly prevalent and important consideration in patients with prostate cancer. In our patient population we found that baseline DEXA scores of 96 patients suggested osteoporosis (T--Score <-2.5) in 64.5% cases and osteopenia (T--Score between -1.5 to -2.5) in 29% cases leaving a small percentage of patients (6.2%) with normal bone health status. A study by Agarwal et al. in Indian patients showed significant loss of

bone mineral density after orchidectomy (13% at 6 months and 18% at 1 year), which results in an increased incidence of osteoporosis from 24-48% at 6 months after performing orchidectomy (12). Bone health in cancer prostate is often a neglected aspect even in present era especially in developing nations.

The current study shows that there was significant improvement in mean BMD (T-score) in 64-patients post ZA therapy at 12-months (at femoral total, femoral neck and spine, 0.95, 0.79 and 0.68, respectively) ($p < 0.05$) while there was significant deterioration in mean BMD at 12-months (at spine, femoral neck and femoral total, -0.77, -0.55 and -0.66, respectively) in 32 patients who did not receive ZA and were on ADT ($p < 0.05$). Kapoor et al., 2011, (13) concluded in a study of 41 patients with non-metastatic cancer prostate patients on ADT, that 3 monthly administration of Zoledronic acid for 1 year improved vertebral and left femoral neck BMD in men on GnRH-agonist treatment. They noticed that alteration in vertebral and left femoral neck BMD was significantly higher in Zoledronic acid therapy group than in the placebo group. Saad et al. (14) studied the effect of Zoledronic acid therapy on skeletal complications in 643 carcinoma prostate patients with bony metastases. Administration of ZA (4mg or 8mg, 3 weekly) reduced the fracture events and increased the median time to first SRE in their study. We also found that administration of monthly Zoledronic acid (4mg) decreased the SRE in our cohort as compared to non-therapy group ($P < 0.002$).

The pain score was measured at baseline and follow-up showed a decreased from mean of 5.1 at baseline to around 2.2 at follow-up i.e. a 2.9 point improvement in subjective perception, from moderate to mild pain in patients who received injection of Zoledronic Acid. When the group which did not receive the therapy was compared at baseline and follow-up, there was significant deterioration in their pain levels with pain scores showing an increase from a mean of 2.81 to 4.41 at the time of follow-up. When the change in pain score between the treatment groups was compared with no treatment, it was found to be significantly better in the therapy group. A Cochrane review of 3682 patients with substantial proportion of pain relief pooled data (eight studies) demonstrated the benefits in the Zoledronate treatment group (15). Study by Saad et al. as mentioned previously showed that patients who received Zoledronic acid had lower mean pain scores (Brief Pain Inventory composite score) as compared to placebo group at every time point and these differences were found to be statistically significant at the 3 and 9 months time points.

There are few limitations in the present study. The study measured bone health and pain scores till 12-months duration and depict data from a single centre only. Secondly, it was not a randomized study and patients with higher risk were the ones who received ZA. Thirdly, follow-up and compliance to treatment is poor amongst few patients in the study due to complicated disease dynamics in a developing country with poor socio-economic status, lack of nearby healthcare facilities and lack of medical insurances. Health care provider and treating physician should be aware of these obstacles in developing and underdeveloped population and all these factors need to be addressed by concerned authority for improving both quantity and quality of these patients.

To the best of our knowledge, this is the first study from India which focuses on bone health in cancer prostate patients and has studied the effect of Zoledronic Acid in Indian population. Bone health becomes all the more important for this population subgroup as we found that most of the patients presenting to us have a high burden disease with very high PSA levels, high grade disease and positive bony metastases and needs further emphasis for improving their overall quality of life.

CONCLUSIONS

Bone-directed therapy (Zoledronic acid) improves the bone health of the patients both objectively and subjectively as assessed by DEXA Scan and pain scores, respectively. Since major cause of morbidity in prostate cancer is bony metastases, bone health must be taken in to account in routine clinical practice as per the standard guidelines.

ACKNOWLEDGMENTS

I acknowledge the cooperation of residents of Urology department of King George's medical university who participated in data collection and evaluation of the patient. We also appreciate the commitment and compliance of the patient who reported the required data.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Huncharek M, Haddock KS, Reid R, Kupelnick B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. Am J Public Health. 2010;100:693-701.
2. Ali I, Waseem A, Wani, Saleem K. Cancer scenario in India with future perspective. Can Ther 2011;8:56-70.
3. Singh AN, Kirti, Dalela D, Sankhwar SN, Natu SM, Srivastava AN. Diagnosis and progression of Prostate Cancer in North Indian population: An affect of Body Mass Index and Age. J Adv Res Biol Sci 2013;5:2569.
4. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71:630-642.
5. [No Authors] Clinical Trials Registry – India. Available at. <http://ctri.nic.in/Clinicaltrials/main1.php?EncHid=45518.80473>.
6. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94:149-58.
7. Hariharan K, Padmanabha V. Demography and disease characteristics of prostate cancer in India. Indian J Urol. 2016;32:103-8.
8. Vinjamoori AH, Jagannathan JP, Shinagare AB, Taplin ME, Oh WK, Van den Abbeele AD, et al. Atypical metastases from prostate cancer: 10-year experience at a single institution. AJR Am J Roentgenol. 2012;199:367-72.
9. Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst. 2012;104:1335-42.
10. Newcomer LM, Stanford JL, Blumenstein BA, Brawer MK. Temporal trends in rates of prostate cancer: declining incidence of advanced stage disease, 1974 to 1994. J Urol. 1997;158:1427-30.
11. Gallina A, Chun FK, Suardi N, Eastham JA, Perrotte P, Graefen M, et al. Comparison of stage migration patterns between Europe and the USA: an analysis of 11 350 men treated with radical prostatectomy for prostate cancer. BJU Int. 2008;101:1513-8.
12. Agarwal MM, Khandelwal N, Mandal AK, Rana SV, Gupta V, Chandra Mohan V, et al. Factors affecting bone mineral density in patients with prostate carcinoma before and after orchidectomy. Cancer. 2005;103:2042-52.
13. Kapoor A, Gupta A, Desai N, Ahn H. Effect of zoledronic Acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog. Prostate Cancer. 2011;2011:176164.
14. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94:1458-68.
15. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst Rev. 2002;(2):CD002068.

Correspondence address:
Ashish Sharma, MD
Department of Urology
King George's Medical University
Lucknow, Uttar Pradesh, 226003, India
E-mail: ashishuc343@gmail.com

ORIGINAL ARTICLE

Vol. 46 (3): 374-380, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0162

Profile of sexuality and symptoms of lower urinary tract in non-institutionalized elderly

Khaled Ahmed Taha [1], Flavio Trigo Rocha [2, 3], Lisias Castilho [4]

[1] Hospital Augusto de Oliveira Camargo, Idaiatuba, SP, Brasil; [2] Centro de Incontinência Urinária, Hospital Sirio Libanes, São Paulo, SP, Brasil; [3] Faculdade de Medicina, Universidade de São Paulo, Urologia, São Paulo, SP, Brasil; [4] Faculdade de Medicina de Jundiai, Jundiaí, SP, Brasil

ABSTRACT

Introduction: Urinary or sexual dysfunction in the elderly are underreported. However, they are highly prevalent. This study aims to identify the prevalence of these conditions.
Objective: The aim is to carry out an investigation in non-institutionalized individuals over 60 years of age, to obtain data on its sexual and urinary health in São Paulo, Campinas, Santo André and Londrina.
Results: 6.000 questionnaires were distributed, and 3425 were included in the study, for the analysis of the questionnaires separately. In relation to ADAM, 92% of the 1385 evaluated were suspicious of androgen deficiency (ADAM). As for the male sexual function, it was observed 37% of premature ejaculation. As for the female sexual function, 1300 (74%) did not practice sexual intercourse and the main reasons were: lack of partner and lack of sexual desire. In addition, 988 (78%) of women who had no sexual intercourse responded that they didn't want sex and, more importantly, about 22% of them would like to have sexual intercourse. International prostate symptom score (IPSS) showed gradual worsening of urinary symptoms with increasing age, being the most prevalent: nocturia and urinary urgency. As for the female IPSS, we noted that even after 80 years, the majority have mild symptoms related to voiding dysfunction; with increasing age there is a gradual increase in the result of the IPSS.
Conclusion: Due to the large number of sexual and urinary disorders found, we recommend the improvement in health conditions, promoting a better quality of life in the elderly.

ARTICLE INFO

Khaled Taha Neto
http://orcid.org/0000-0002-8497-9679

Keywords:
Women; Lower Urinary Tract Symptoms; Erectile Dysfunction

Int Braz J Urol. 2020; 46: 374-80

Submitted for publication:
March 25, 2019

Accepted after revision:
August 18, 2019

Published as Ahead of Print:
September 30, 2019

INTRODUCTION

Sexual Function

The definition of erectile dysfunction (ED) was proposed in 1992, during a conference on impotence, being that the inability of achieving or maintaining an erection for a satisfying sexual relation.

Men with hypogonadism show few symptoms, and are frequently not diagnosed, denied by the patient and not evidenced by the doctor, affecting more than 10% of population (1). In a survey by Hospital das Clinicas in São Paulo, individuals submitted to prostate cancer screening showed a global prevalence of ED of 66% (2).

Sexual Disfunction affects around 152 million of men worldwide. In 2025, around 322 million of men are estimated to present ED. The direct costs with treatment in the United States (US) are estimated in 400 million dollars yearly (3).

Premature ejaculation (PE) is the second most prevalent disorder in men, with indicators ranging between 26 and 31%; little variation is found among different age groups, despite being more frequent in young men (4).

Urinary Function

Data from the National and Nutrition Examination suggest that low urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) are common in men over 30, increasing with age (5). Over a follow-up period of 42 months it was observed an increase of the international prostate symptom score (IPSS) values in relation to moderate and major symptoms from 33% to 49% (6). Urinary retention is the final stage of BPH, occurring in 6.8 cases per 1000 individuals, increasing according to age, prostatic size and severity of the symptoms (7).

A method of great value in evaluating micturition dysfunction is the application of the American Urological Association-7 (AUA-7) questionnaire, initially used to assess emptying symptoms and later renamed IPSS. After that, it was considered the score of the life quality of the specific disease. It was also validated to the Portuguese language (8).

The IPSS was initially used to assess urinary symptoms in men with BPH. However, it became evident that IPSS was not specific to disease or gender. Therefore, the validation and use of the IPSS in women are as good as they are in men (9).

According to the National Kidney and Urologic Disease Advisory Board, urinary incontinence (UI) affects 13 million Americans, having an elevated frequency among elderly people (10-35%), representing US$ 11 billion from the government expenses (10).

It is estimated that 50 million people worldwide suffer from UI, being that more common in women, affecting up to 50% of them at some point in life (11). In Brazil, it is estimated that up to 23% of the female population is incontinent, and, in elderly women, this prevalence can vary between 8 to 35% (12).

In 2002, the International Society of Continence established overactive bladder (OB) as a syndrome characterized by symptoms of urgent urination, with or without incontinence, usually with nocturia and increase of urinary frequency, with a prevalence of 34 million of individuals, most of them elderly people, with costs of US$ 12 billion per year.

OBJECTIVE

To conduct an investigation of a non-institutionalized elderly population, of both sexes, in order to obtain data related to the prevalence of sexual and urinary dysfunction.

MATERIALS AND METHODS

We assessed the prevalence of sexual and urinary dysfunction of these individuals by means of a validated questionnaire or in validation stage (e.g ADAM questionnaire).

It was performed an active search of respondents through phone books of the cities, to ensure that these elderly individuals were a reliable sample of the Brazilian population not linked to any medical service. There was home delivery of these questionnaires, with explanation and signature of the consent form. After seven days, the researches collected these documents.

Inclusion criteria: male or female, with age equal to or above sixty, non-institutionalized, capable of comprehending the study

Exclusion criteria: the ones who had difficulties in understanding the goals, illiterate people or unable to answer without help and questionnaires answered incorrectly.

Applied questionnaires: income (income assessment according to the number of monthly minimum wage received), androgen deficiency in the aging male (ADAM) questionnaire (elderly screening questionnaire for evaluation of androgenic disorder), erectile dysfunction questions based on the Study on the Sexual Life of the Brazilian, by Carmita Abdo (a research that turned into a book, about the Brazilian sexual habits, in a simple and objective language, mentioning various topics like: sexual orientation, erectile dysfunction, orgasm, sexual desire and sexually transmitted diseases and the IPSS (questionnaire

that evaluates the urinary symptoms and that can be used on both men and women). In relation to premature ejaculation, it was explained to the interviewee the definition and asked if he has frequent or occasional premature ejaculation.

Statistical analysis

Descriptive analysis with presentation of absolute and relative frequency tables for categorical variables and dispersion measures for numerical variables.

For comparison of proportions we used the chi-square or the Fisher's exact test, when necessary.

The significance level adopted for the statistical tests was 5%.

RESULTS

From the 6000 distributed questionnaires, 2575 were excluded, and 3425 were analyzed. 1575 male and 1850 female questionnaires were reviewed. In relation to family income, we found 80% individuals from classes D (between two and four minimum wages) and E (less than two minimum wages).

Regarding the age of the elderly, the average age of respondents was 70 years, 69.8 years among men and 70.1 years among women.

Sexual Function

One thousand three hundred and eighty-five ADAM questionnaires were analyzed. In relation to question 1 (reduction in libido) and 7 (erection failure) which separately make up a positive result, we obtained 69% of YES as an answer for question 1 and 79% for question 7. It was observed a total positive of 92%, with a gradual increase according to increase in age (Figure-1).

In relation to PE, from the 1220 respondents, 37.5% presented premature ejaculation, and, in addition, 24.7% also occasionally presented PE (Figure-2).

Assessing the number of intercourse in 1755 women, we have identified that more than 90% have none or report to have less than 5 sexual intercourse per month (Figure-3).

The main reasons for the lack of sexual intercourse are: lack of partner and sexual desire. 988 people (78%) answered that they do not want sexual intercourse, and, most important, 272 people (22%) do not have but would like to have sexual intercourse.

Figure 1 - ADAM Questionnaire-Total positive: 92%.

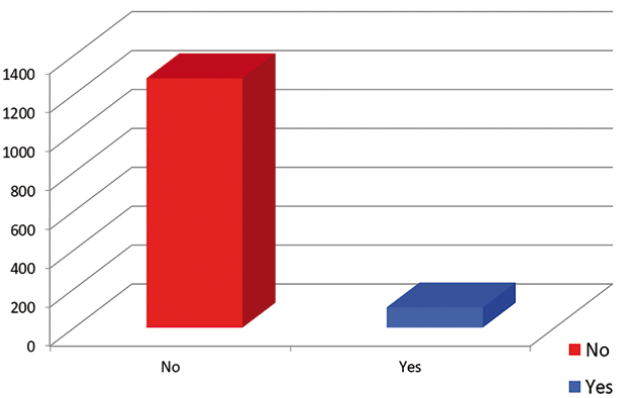


Figure 2 - Results of premature ejaculation.

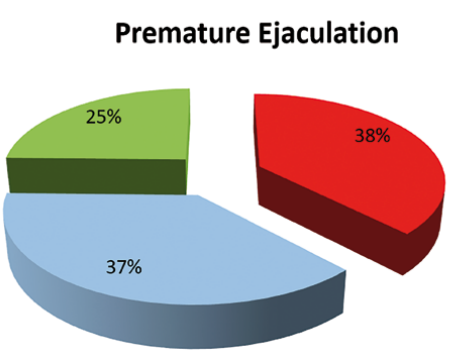
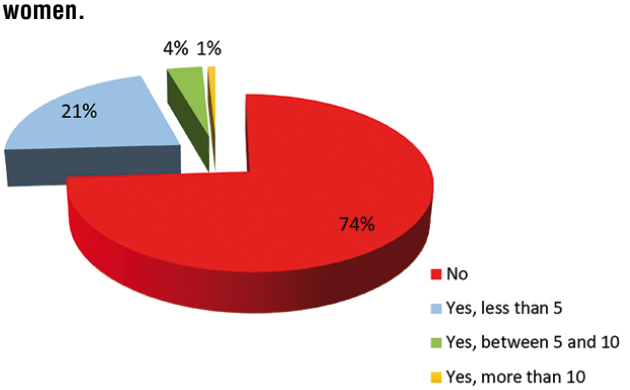


Figure 3 - Result of the monthly sexual intercourse of women.



Male IPSS

One thousand four hundred and sixty-five questionnaires were analyzed, with average age of 69.8 years (60-95). The main identified symptoms were respectively: nocturia, frequency lower than 2 hours, urgency, weak stream, incomplete emptying, intermittence and micturition effort, occurring a worsening of the micturition pattern, with more major and moderate symptoms with aging. (Table-1).

Female IPSS

One thousand sixty seventy eight questionnaires were analyzed, with average age of 70.1 years (60-99). The main symptoms were, respectively: urgency, frequency lower than 2 hour, nocturia, weak stream, incomplete emptying, intermittence and micturition effort.

Even after 80 years of age, most women showed minor symptoms, with a gradual worsening of the IPSS with aging (Table-2).

Urinary Incontinence

From the 3327 respondents, 853 (25.63%) presented regular leaking of urine, being more common in women than in men (Table-3).

Additionally, from the 3347 respondents, 419 (12%) elderly people used some kind of method of protection from leaking in a regular way. Regular usage was observed in 21% of women and 3% of men (Table-4).

DISCUSSION

In Brazil, the statute of the elderly define elderly being the individual aged sixty or over. However, in most other countries, the elderly are those aged sixty-five and over, making it difficult the comparison of papers.

Geriatric disfunctions are under-reported since the elderly are afraid of exposing themselves and being mis-interpreted. Sexual and urinary dysfunctions are associated with many social and psychological losses, with worsened quality of life.

According to data from Brazilian Institute of Geography and Statistics (2013), there are 201 million people living in Brazil, from these, approximately 13% are elderly people. The number of elderly people grows throughout the years, from 2.4% of the Brazilian population in 1940 to 13% in 2013.

Table 1 - Result of IPSS in men.

IPSS	60-64	65-69	70-74	75-79	≥ 80	Total
Mild (0-7)	347 (76.77)	201 (58.43)	183 (62.24)	109 (49.10)	73 (47.71)	913 (62.32)
Moderate (8-19)	76 (16.81)	113 (32.85)	86 (29.25)	85 (38.29)	57 (37.25)	417 (28.46)
Severe (20-35)	29 (6.42)	30 (8.72)	25 (8.50)	28 (12.61)	23 (15.03)	135 (9.22)
Total	**452**	**344**	**294**	**222**	**153**	**1465**

Table 2 - Result of IPSS in women.

IPSS	60-64	65-69	70-74	75-79	≥ 80	Total
Mild (0-7)	366 (69.32)	264 (67.52)	192 (60.95)	133 (56.36)	111 (53.37)	1066 (63.53)
Moderate (8-19)	141 (26.70)	114 (29.16)	99 (31.43)	85 (36.02)	78 (37.50)	517 (30.81)
Severe (20-35)	21 (3.98)	13 (3.32)	24 (7.62)	18 (7.63)	19 (9.13)	95 (5.66)
Total	**528**	**391**	**315**	**236**	**208**	**1678**

Table 3 - Prevalence of urinary incontinence.

Incontinence	Woman	Man
No	1194	1280
Yes, 1 or 2 days/week	361	180
Yes, 3 or 4 days/week	90	30
Yes, 5 or more days/week	149	43
Total	**1794**	**1533**

Table 4 - Prevalence of elderly who use methods of protection from urinary leaking.

Use methods of protection	Woman	Man
No	1438	1490
Yes, 1 or 2 days/week	134	22
Yes, 3 or 4 days/week	34	2
Yes, 5 or more days/week	202	25
Total	**1808**	**1539**

In a recent metanalysis that analyzed 76 articles assessing the erectile dysfunction in elderly, it was evidenced that lack of sexual desire was mentioned by 12-51% of the elderly over 60 years, 20-65.9% for over 70 years and 40-82% for over 80 years. Those bothered with erectile dysfunction were 14.3-70% in elderly over than 60 years, 6.7-48% for over 70 years and 38% for over 80 years. And only a small portion of this population seeks medical help or use medicines for the improvement of this problem (13).

The ADAM questionnaire is a screening form to be used in individuals over 40, showing great sensitivity (85%) and specificity (19-60%) and is an acceptable tool to monitor the therapeutic development with hormone replacement. Low specificity can be a result of the high prevalence of psychological symptoms that are not addressed in the questions (14). Furthermore, a correlation was found between having a positive ADAM score and both increased stress levels ($p < 0.001$) and poor sleep quality ($p < 0.001$), with stress displaying the strongest effect (15).

Therefore, there can exist 10.5 million of individuals who present ADAM and are in their homes, without medical follow-up.

Tancredi et al. (16), in relation to the ADAM questionnaire, identified 50% of positive answers for the reduction in libido and 59% in relation to weaker erections. Blümel et al. (14) found in the question about reduction of libido a sensitivity of 63% and specificity of 67% and, in relation to the question about ED, they found a sensitivity of 67% and specificity of 53%. In our work, we found greater positivity in the answers, reflecting a precarious medical assistance provided to the elderly people, especially concerning sexual complaints.

In relation to the sexual function of elderly women, we found in our study 78% of the 1260 with no sexual intercourse and lack of desire, similar to literature, in which 73% presented lack of sexual desire (4). The information of greatest importance is the fact that 22% of these elderly women who have no sexual intercourse, would like to have it. Considering the existence of 15 million elderly women in Brazil, there can be more than 3.2 million elderly women with no sexual intercourse but that would like to have it, and should be better assessed.

In relation to the causes that harm the sexuality of elderly women, many authors have different opinion. Ballone (17) mentions that the main problem for sexual dysfunction in elderly women is dyspareunia. Abdo et al. (4) claims that dyspareunia reduces with aging, having the lack of sexual desire as the main disorder. We have identified dyspareunia as the less common cause for the lack of sexual relation, the main causes are: lack of partner and lack of sexual desire.

We evidenced a predominance of urinary symptoms related to storage, in both sexes. There is a significant worsening in men with aging and in women the minor symptoms prevail in all ages. We should always take into consideration factors of confusion such as: hypertension, diabetes, neurological diseases and use of diuretic.

Rodrigues et al. (18), in a study involving 400 men with BPH, in which 36% of the elderly men were between 60 and 69 years old and 44% being more than 70, presented moderate or major symptoms, similar to what was found in our work. We found 40% of elderly men with IPSS higher than 8, corresponding to approximately 4.6 million of elderly men which will need treatment.

Despite the fact that there are not many studies on female urinary dysfunction, the prevalence of LUTS is 3-23%. The main causes are: stress incontinence (51%), overactive bladder (26%), followed by the difficulty in the urinary emptying (18).

Choi et al. (19), examining the IPSS in 1415 women, found a prevalence in voiding symptoms about 9%, with greater predominance of obstructive symptoms, differently from what was observed in literature and in our work.

Yoo et al. (20), researched the urinary symptoms, through the International Continence Society and the IPSS in the population of South Korea over 40 years old and identified a prevalence of LUTS in 68%, increasing significantly with the years in both men and women. The most common symptoms mentioned were: nocturia, frequency and weak stream. And the IPSS showed that, at least 40%, had moderate symptoms, similar to what was observed in our study.

Concerning OB, a work from college of Porto, found a greater prevalence in men (35%) than in women (29%). In the United States, according to the NOBLE study (21) the global prevalence was similar in men and women (17%). In our work, we found data different from the literature, in which elderly women (28%) showed greater prevalence of OB, corresponding to approximately 4.8 million of elderly women. Despite OB shows greater frequency with aging, it should not be perceived as a part of the aging process, but should be treated instead.

Therefore, there is a great prevalence of OB in the elderly, and, when associated with nocturia, causes several damages such as falls and fractures, with reduction of life span.

Information on UI are divergent and the prevalence in Brazil is almost not mentioned. Menezes et al. (22) found prevalence in non-institutionalized women of 61%. Faria et al. (23), found prevalence of 42% in elderly women. Data on men are scarce and confusing. We found 600 (33%) elderly women and 253 (16%) elderly men who were incontinent.

UI is a distressing and disabling condition, which harms psychological, physical and sexual aspects, becoming an important health problem, due to the social and economic impact on these individual lives.

CONCLUSIONS

Consequently, due to the great number of sexual and urinary disorders found, there is a need of better implementation of public health measures, improving the service and treatment of those, creating a better quality of life for these group of individuals.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Plymate S, Totowa, NJ, Bagatell C, Bremmer W. Hypogonadism. Hypogonadism in men. Androgens in Health and Disease. Humana Press Inc. 2003; pp. 45-75.

2. Barbosa JA, Muracca E, Nakano É, Assalin AR, Cordeiro P, Paranhos M, et al. Interactions between lower urinary tract symptoms and cardiovascular risk factors determine distinct patterns of erectile dysfunction: a latent class analysis. J Urol. 2013;190:2177-82.
3. Seftel AD. Erectile dysfunction in the elderly: epidemiology, etiology and approaches to treatment. J Urol. 2003;169:1999-2007.
4. Abdo CHN, Oliveira JWN, Moreira ED, Fittipaldi JAS. Perfil sexual da população brasileira: resultados do estudo do comportamento sexual (ECOS) do Brasileiro. Rev Bras Med. 2002;59:250-7.
5. Wright JJ, O'Connor KM. Female sexual dysfunction. Med Clin North Am. 2015;99:607-28.
6. Hughes AK, Rostant OS, Pelon S. Sexual Problems Among Older Women by Age and Race. J Womens Health (Larchmt). 2015;24:663-9.
7. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. J Urol. 2005;173:1256-61.
8. Berger M, Luz Junior PN, Brasil SN, Koff WJ. Statistical validation of the international prostatic symptom score (I-PSS) in portuguese. J Bras Urol. 1999;25:225-34.
9. Okamura K, Nojiri Y, Osuga Y, Tange C. Psychometric analysis of international prostate symptom score for female lower urinary tract symptoms. Urology. 2009;73:1199-202.
10. Fantl JA, Newman DK, Colling J. Urinary Incontinence in Adults: Acute and Chronic Management: 1996 Update. Rockville (MD): Agency for Health Care Policy and Research (AHCPR); 1996. Available at. <https://www.ncbi.nlm.nih.gov/books/NBK52169>
11. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61:37-49.
12. Amaro JL, Macharelli CA, Yamamoto H, Kawano PR, Padovani CV, Agostinho AD. Prevalence and risk factors for urinary and fecal incontinence in Brazilian women. Int Braz J Urol. 2009;35:592-7.
13. Geerkens MJM, Al-Itejawi HHM, Nieuwenhuijzen JA, Meuleman EJM, issenberg-Witte BI, van Moorselaar RJA, et al. Sexual Dysfunction and Bother Due to Erectile Dysfunction in the Healthy Elderly Male Population: Prevalence from a Systematic Review. Eur Urol Focus. 2019. [Epub ahead of print]
14. Blümel JE, Chedraui P, Gili SA, Navarro A, Valenzuela K, Vallejo S. Is the Androgen Deficiency of Aging Men (ADAM) questionnaire useful for the screening of partial androgenic deficiency of aging men? Maturitas. 2009;63:365-8.
15. Charlier CM, Barr ML, Colby SE, Greene GW, Olfert MD. Correlations of Self-Reported Androgen Deficiency in Ageing Males (ADAM) with Stress and Sleep among Young Adult Males. Healthcare (Basel). 2018;6.
16. Tancredi A, Reginster JY, Schleich F, Pire G, Maassen P, Luyckx F, et al. Interest of the androgen deficiency in aging males (ADAM) questionnaire for the identification of hypogonadism in elderly community-dwelling male volunteers. Eur J Endocrinol. 2004;151:355-60.
17. Ballone GJ. Sexo nos idosos. PsiqWeb psiquiatria geral [online]. 2015. Available at. <http://psiqweb.net/index.php/depressao-2/depressao-e-disfuncao-sexual/>.
18. Rodrigues P, Meller A, Campagnari JC, Alcântara D, D'Império M. International Prostate Symptom Score--IPSS-AUA as discriminat scale in 400 male patients with lower urinary tract symptoms (LUTS). Int Braz J Urol. 2004;30:135-41.
19. Choi YS, Kim JC, Lee KS, Seo JT, Kim HJ, Yoo TK, et al. Analysis of female voiding dysfunction: a prospective, multi-center study. Int Urol Nephrol. 2013;45:989-94.
20. Yoo TK, Lee KS, Sumarsono B, Kim ST, Kim HJ, Lee HC, et al. The prevalence of lower urinary tract symptoms in population aged 40 years or over, in South Korea. Investig Clin Urol. 2018;59:166-176.
21. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003;20:327-36.
22. Menezes GM, Pinto FJ, da Silva FA, de Castro ME, de Medeiros CR. [Complaint of urinary loss: a silent woman's problem]. Rev Gaucha Enferm. 2012;33:100-8.
23. Faria, Carlos Augusto et al. Incontinência urinária e noctúria: prevalência e impacto sobre qualidade de vida em idosas numa Unidade Básica de Saúde. Rev. bras. geriatr. gerontol. 2014,17,pp.17-25.

Correspondence address:
Khaled Ahmed Taha, MD
Hospital Augusto de Oliveira Camargo
Av. Francisco de Paula Leite, 399
Jardim Santa Cruz, Indaiatuba, 13344-700, SP, Brasil
E-mail: khaledurol@yahoo.com

EDITORIAL COMMENT

Vol. 46 (3): 381-382, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0162.1

Editorial Comment: Profile of sexuality and symptoms of lower urinary tract in non-institutionalized elderly

Valter Javaroni [1]

[1] *Departamento de Andrologia, Hospital Federal do Andaraí, Rio de Janeiro, RJ, Brasil*

COMMENT

The authors conducted a nice survey among elderly in a populacional-base sample, stressing the importance of some urologic under-reported conditions hidden throughout different causes in a population assisted only by public health system (1). They found a huge percentage of elderly men and women with symptoms that could correlate with some diseases, and consequently, motivate search for adequate health assistance in order to reach better quality of life.

Brazil faces a significant increase in the number of older adults. And as the older population grows, this knowledge is usefull for antecipating need for public health resources, expertise and services related to improve quality of life in elderly. Two important aspects that deserve consideration: the definition of sexuality and some limitations of the study. An important indicator of successful ageing is subjective well--being, that is affected by a multitude of factors and is a direct indicator of health outcomes in older adults (2). Sexuality and urinary dysfunctions are major topics for both genders (3).

Sexuality is predominantly recognized only as the sexual act, but specially for elderly has a broader meaning and should include affection, relationships and the erotic and sexual relationship (4). One relevant aspect to consider, in order to stimulate seek for help, also evolves medical education and doctors ability to address this topic (4). Sexual problems are frequent among older adults, but these problems are infrequently discussed with physicians, particularly in women (5).

The questions presented to the interviewees were not shown, as well as some answers. Pathologies such as premature ejaculation, hypogonadism and overactive bladder received unclear diagnostic criteria. The lack of a control group and some variables prevents further analysis of their results. Body mass index, marital status, education categories, physical activity, religion, comorbidities, medicines, prior surgery, social and familial relationships, quality of life impact, Sexualy Transmited Disease knowledge, already proved some influence (4) over authors objectives.

Finnaly, as the number of individuals who tried to seek medical assistance was not researched, perhaps the proposal to reverse the situation should include basic education in health, training of health professionals and also proactive policies that bring patients closer to solutions. But without a doubt, the articule provides additional evidence to support the claim for better public health services that identify and treat men and women with modifiable conditions, contributing to improve well being during ageing.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Taha KA, Rocha FT, Castilho L. Profile of sexuality and symptoms of lower urinary tract in non-institutionalized elderly. Int Braz J Urol. 2020;46:374-80.
2. Odlum M, Davis N, Owens O, Preston M, Brewer R, Black D. Correlates and aetiological factors associated with hedonic well-being among an ageing population of US men and women: secondary data analysis of a national survey. BMJ Open. 2018;8:e020962.
3. Lindau ST, Gavrilova N. Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing. BMJ. 2010;340:c810.
4. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357:762-74.
5. Rubin ES, Rullo J, Tsai P, Criniti S, Elders J, Thielen JM, Parish SJ. Best Practices in North American Pre-Clinical Medical Education in Sexual History Taking: Consensus From the Summits in Medical Education in Sexual Health. J Sex Med. 2018;15:1414-25.

ARTICLE INFO

Valter Javaroni
https://orcid.org/0000-0003-3877-0601

Int Braz J Urol. 2020; 46: 381-2

Valter Javaroni, MD

Departamento de Andrologia,
Hospital Federal do Andaraí,
Rio de Janeiro, RJ, Brasil
E-mail: drjavaroni2000@yahoo.com.br

Submitted for publication:
January 10, 2020

Accepted after revision:
January 15, 2020

ORIGINAL ARTICLE

Vol. 46 (3): 383-389, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0212

Efficacy of Leuprorelide acetate (Eligard®) in daily practice in Brazil: a retrospective study with depot formulations in patients with prostate cancer

Carla S. M. de Freitas [1], Aleida N. Soares [2]

[1] Hospital do Câncer de Muriaé, MG, Brasil; [2] Instituto de Ensino e Pesquisa da Santa Casa de Belo Horizonte, Belo Horizonte, MG, Brasil

ABSTRACT

Introduction: Androgen deprivation therapy (ADT) is the mainstay of therapy for advanced prostate cancer. Studies addressing the efficacy of different depot formulations of long acting luteinizing hormone releasing hormone agonists in the Brazilian population are lacking. We aimed to compare the efficacy of three schedules of leuprolide acetate in lowering PSA in a real world population.
Materials and Methods: We reviewed the medical records of patients with prostate cancer seen at our institution between January 2007 and July 2018. We analyzed patients treated with long-acting leuprolide acetate and grouped these patients into three strata according to the administration of ADT every 1, 3 or 6 months. The primary outcome was the serum prostate specific antigen (PSA) levels at 6 and 12 months after treatment initiation. We used Friedman test to compare the distribution of PSA levels at baseline and at 6 and 12 months within each treatment stratum. We considered two-sided P values <0.05 as statistically significant. We analyzed toxicity descriptively.
Results: We analyzed a total of 932 patients, with a median age of 72 years and a median time since diagnosis of prostate cancer of 8.5 months. ADT was administered monthly in 115 patients, quarterly in 637, and semiannually in 180. Nearly half of the patients had locally advanced disease. In comparison with baseline, median serum PSA levels were reduced at 12 months by at least 99.7% in the three strata (P <0.001 in all cases). Sexual impotence and hot flashes were the most frequently reported toxicities.
Conclusion: To our knowledge, this is the largest assessment of real-world data on alternative schedules of leuprolide in a Brazilian population. Our study suggests that PSA levels can be effectively be reduced in most patients treated with monthly, quarterly, or semiannual injections of long-acting leuprolide acetate.

ARTICLE INFO

Carla S. M. de Freitas
https://orcid.org/0000-0002-9397-9777

Keywords:
Prostatic Neoplasms; agonists [Subheading]; Prostate-Specific Antigen

Int Braz J Urol. 2020; 46: 383-9

Submitted for publication:
March 29, 2019

Accepted after revision:
November 01, 2019

Published as Ahead of Print:
December 30, 2019

INTRODUCTION

According to GLOBOCAN, it is estimated that 1.276.106 men were diagnosed with prostate cancer worldwide in 2018, with an expect 6.3% increase in incidence for the year of 2020 (1-3). By the year 2030, the burden from prostate cancer in Central and South America is expected to nearly double as a result of population growth and aging, moreover, increased early detection and public awareness are likely to lead to further increase in incidence in this world region (4). In

Brazil, prostate cancer is the most frequent non-cutaneous tumor and the second leading cause of death from cancer in men (5).

Given the androgen dependence that characterizes prostate cancer, androgen deprivation therapy plays a key role in distinct phases of the disease. Among patients with advanced disease, androgen deprivation is the mainstay of therapy for both hormone-sensitive and castration-resistant prostate cancer (6), with long-acting luteinizing-hormone-releasing hormone (LHRH) agonists being currently the main form of achieving androgen deprivation (7). Most patients treated with a LHRH agonist achieve castrate testosterone levels similar to those found after bilateral orchiectomy (8). As a result of testosterone suppression, disease control can be achieved in the majority of patients as indicated, for example, by decreased levels of prostate specific antigen (PSA). Clinical trials of different LHRH agonists have demonstrated the efficacy of these agents in different settings. In particular, the efficacy and safety of Eligard® (a depot formulation of leuprolide acetate for subcutaneous injection every 1, 3 or 6 months) have been assessed and confirmed in clinical trials (9, 10). However, such studies are often limited by strict selection criteria, and a need remains for "real-world" data collected in observational studies (9-14).

OBJECTIVES

In the current study, we sought to investigate the efficacy of Eligard® used monthly, quarterly and semiannually, in a heterogeneous population of patients from routine clinical practice at the Muriaé Cancer Hospital, state of Minas Gerais, Brazil.

MATERIALS AND METHODS

Study design and patient eligibility

The study protocol was reviewed and approved by the Institutional Ethics Committee, and written informed consent was waived due to the observational nature of the investigation. In this retrospective study, we reviewed the medical records of 932 patients with prostate cancer seen at our institution between January 2007 and July 2018. Given the observational nature of the study, diagnostic and treatment decisions, including the choice of androgen deprivation therapy, formulation and schedule, as well as use of concomitant medication, were at the discretion of the attending physicians.

Eligible patients were men with prostate cancer, aged ≥18 years old, and treated with Eligard® (henceforward referred to as androgen deprivation) at some point during the study period. We included in this study all the patients who had baseline serum PSA results. We grouped patients into three separate strata according to the administration of androgen deprivation therapy every 1, 3 or 6 months.

Data collection, outcomes of interest, and statistical analysis

We collected data on demographic patient characteristics, features of prostate cancer, dates and clinical events related to treatment, serum PSA results, and toxicity. The primary outcome measure was the serum PSA levels at 6 months and 12 months after treatment initiation. After using the Kolmogorov-Smirnov test to demonstrate that PSA levels did not have normal distribution, we used Friedman test to compare, within each treatment stratum (monthly, quarterly, or semiannually), the distribution of PSA levels at baseline and at 6 and 12 months. Moreover, we used Wilcoxon's rank sum test to make pairwise comparisons between adjacent time points within strata. We made no comparisons between strata. We considered two-sided P values <0.05 as statistically significant and performed the analyses with SPSS, version 22.0.

RESULTS

Patient characteristics

A total of 932 patients fulfilled the selection criteria and were analyzed, with their key characteristics being displayed in Table-1. The median age was 72 years (interquartile range, 65 to 78 years). Comorbidities were reported in 43.8% of the study population, most of which cardiovascular (85.0%). The median time since diagnosis of prostate cancer was 8.5 months, with 598

Table 1 - Patient characteristics (n=932).

Characteristic	Value
Age, years	
Median (interquartile range)	72 (65 to 78)
Time since diagnosis of prostate cancer in months	
Median (interquartile range)	8.5 (5 to 26)
Ethnicity	
White	307 (32.9%)
Black	619 (66.5%)
Not available	6 (0.6%)
Gleason score	
Low	320 (34.3%)
Intermediate	318 (34.1%)
High	274 (29.4%)
Not available	20 (2.1%)
Prostate cancer stage at diagnosis	
I	35 (3.8%)
II	369 (39.6%)
III	269 (28.9%)
IV	218 (23.4%)
Not available	41 (4.4%)
Treatment	
Radical prostatectomy	163 (17.5%)
Transurethral resection of the prostate	72 (7.7%)
Radiotherapy	588 (63.1%)
RT locally advanced	235 (39.9%)
RT rescue	104 (17.7%)
RT adjuvant	122 (20.7%)
RT palliative	127 (21.7%)
Chemotherapy	52 (5.6%)
Not available	57 (6.1%)

(64.2%) patients being diagnosed ≤12 months and 158 (17.0%) >4 years. The Gleason score was distributed relatively evenly between, low (Gleason ≤6), intermediate (Gleason 7) and high (Gleason ≥8) grade, and nearly three quarters of patients had non-metastatic disease. Bone metastases were reported in 161 (74%) of the patients in stage IV, while 5 patients (2.3%) had metastases at other distant sites and 12 (5.5%) had lymph node metastases. Radiotherapy and radical prostatectomy were the most frequent treatment modalities, in the beginning of the use of Eligard®.

Indication for androgen deprivation

Androgen deprivation therapy was administered monthly in 115 patients, quarterly in 637, and semiannually in 180. Overall across strata, 711 (76.3%) of the patients were treated concomitantly with other modalities, and 129 (13.8%) patients had received previous hormone therapy for the underlying disease. Nearly half of the patients were considered to have locally advanced prostate cancer, and this was the main indication for androgen deprivation. There was biochemical recurrence after prostatectomy in 104 of the 235 (44.3%) patients who underwent prostatectomy and in 122 (20.7%) of the 588 treated with radiotherapy. RT locally advanced (235, 39.9%), rescue radiotherapy 104 (17.7%), adjuvant radiation therapy 122 (20.7%), palliative radiotherapy 127 (21.7%).

Among the 932 patients, 803 (86.2%) were treated with the LHRH agonist alone, while 129 (13.8%) of the patients received it in combination with an antiandrogen (bicalutamide [8.4%], flutamide [4.8%], or cyproterone acetate [0.6%]).

PSA levels

Table-2 presents summary results for the serum PSA levels in each stratum at the three time points of interest. In comparison with baseline, median serum PSA levels were reduced at 12 months by at least 99.7% in the three strata (arrows in Figure-1). As shown in Figure-1, all pairwise comparison between adjacent time points within strata were statistically significant, with the exception of the comparison between 6 and 12 months for the monthly administration.

Safety and tolerability

A total of 72 (7.7%) patients reportedly had treatment-associated toxicity registered in the medical records. Among these cases, sexual impotence and hot flashes were the most frequent

Table 2 - Serum prostate specific antigen (PSA) levels versus leuprolide schedule.

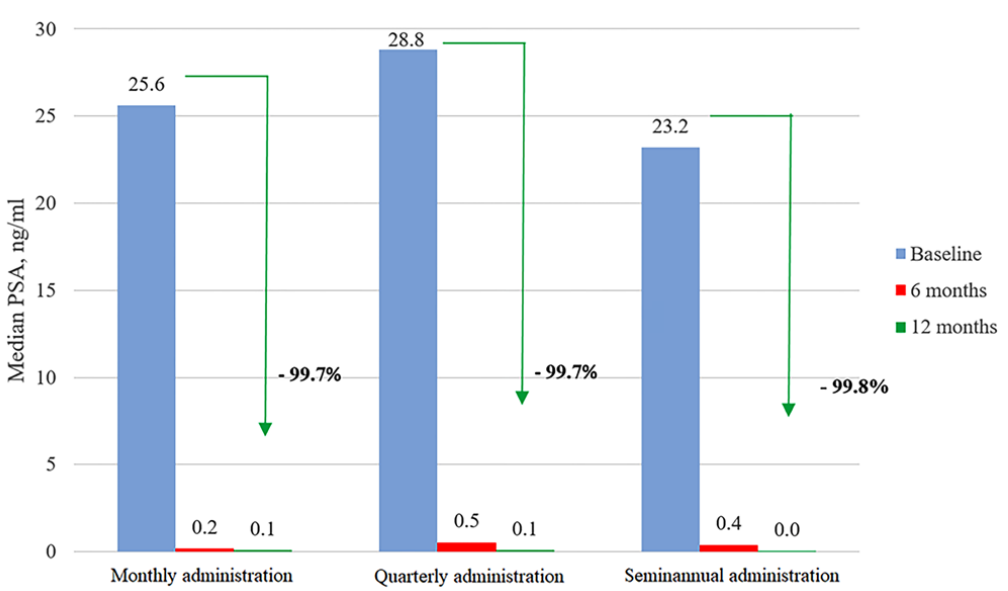
Stratum	Median PSA (interquartile range), ng/mL			P value
	Baseline	6 months	12 months	
Monthly	n=115	n=108	n=104	<0.001
	25.6 (13.7 to 86.0)	0.18 (0.05 to 1.6)	0.08 (0.1 to 0.7)	
Quarterly	n=637	n=588	n=512	<0.001
	28.8 (13.0 to 87.0)	0.54 (0.05 to 3.59)	0.09 (0.01 to 1.0)	
Semiannualy	n=180	n=151	n=103	<0.001
	23.2 (9.4 to 70.5)	0.39 (0.04 to 2.08)	0.04 (0.01 to 0.37)	

and were reported in 58 (6.2%) and 23 (2.5%) patients, respectively. More severe toxicity that was possibly associated with treatment was reported in only 9 (0.9%) of patients: there were two cases of hemorrhagic stroke, and one case each of heart failure secondary to coronary insufficiency, peripheral vascular insufficiency, angina, pulmonary embolism, and acute myocardial infarction. Despite this potential association with treatment, all these cases had comorbidity whose causal link with the toxicity could not be ruled out by chart review. In many cases, treatment for the comorbidity was reportedly used irregularly by the affected patients. No patient reportedly discontinued treatment prematurely due to toxicity.

DISCUSSION

To our knowledge, the current study is the largest reported assessment of real-world data on patients with prostate cancer in Brazil. The study confirms the effectiveness and safety of this depot

Figure 1 - Median levels of serum prostate specific antigen (PSA) in each stratum over time.



formulation of leuprolide acetate in clinical practice. Effectiveness was assessed on the basis of serum PSA declines during the first year of treatment, and safety was ascertained on the basis of toxicity reported in the medical records. Although the reliability and state of completion of medical records are well-known limitations of retrospective studies, the toxicity profile disclosed by our study overlaps with the profile of adverse events reported in clinical trials. On the other hand, the PSA data are objective and were available for the vast majority of time points. As a result, we believe our results add to the current literature by confirming the effectiveness of this LHRH agonist and the validity of a flexible approach, in terms of the choice of administration schedule, which may suit individual patients and clinicians according to their priorities.

Three other observational studies have been conducted with the objective of evaluating the effectiveness, tolerability and/or impact on the quality of life of this depot formulation of leuprolide acetate in daily clinical practice among patients with prostate cancer. In the ELIRE study, conducted in France, the formulation used was for administration every 3 or every 6 months (11). Among 1.853 registered patients, the mean age was 75 years, and the mean time to diagnosis was 7 months. Interestingly, the criteria for choosing between the quarterly or semiannual administration were different, with patients using the latter schedule being more likely to be older and less autonomous than those using the former. The authors concluded that semiannual administration provides more flexibility in the management and follow-up of patients with locally advanced or metastatic prostate cancer. The results suggest that the semiannual use of the LHRH agonist is as effective as the other regimens, resulting in a difference in treatment cost between groups, impacting positively on Brazilian public health. The MANTA study, conducted in Belgium, assessed both a monthly and a quarterly schedule in 243 patients and confirmed that both depot formulations of leuprolide acetate are well tolerated and reliably lowered serum PSA and testosterone levels in routine clinical practice (13). Finally, a study in Germany assessed the administration of leuprolide acetate every 6 months in 1.273 patients (12). At 12 months, there was a median reduction of 96% (to 0.5ng/mL) in serum PSA levels. Interestingly, further PSA and serum testosterone decreases were observed in a subpopulation of patients treated initially with other LHRH analogues and who switched to 6-monthly leuprolide acetate. Similar to the present study, toxicity was reported in the German study in 9% of patients, and the majority were not considered serious. Of note, this LHRH agonist was found to be the most frequently used form of medical castration in another study from Germany, in this case based on a claims database (15).

Clinical trials usually demonstrate the efficacy and tolerability of therapeutic agents in relatively homogeneous populations of patients meeting strict selection criteria. Real-world studies are important because they have broader criteria and may include far more patients in populations that are likely to be observed in routine clinical practice. Compared with patients enrolled in clinical trials (9, 10), patients in observational studies usually display larger variability in tumor staging, Gleason scores, indications for androgen deprivation, and comorbidity. Many of the patients analyzed in observational studies, including ours, would have been excluded from clinical trials (11-13). Reassuringly, however, the results of clinical trials and observational studies with this LHRH analogue overlap to show that PSA levels can be effectively reduced in most patients treated with monthly, quarterly, and semiannual injections.

Our study did not aim at formally to compare the effectiveness or tolerability of the three schedules of administration of this LHRH analogue. Nevertheless, the results show that median serum PSA levels were reduced by at least 99.7% across the three strata, with no notable differences among them. Moreover, these results were seen in spite of the fact that most patients received the LHRH analogue alone, unlike in some studies, in which variable proportions of patients were treated with combinations containing an anti-androgen, a bisphosphonate, or chemotherapy. In such a heterogeneous population as ours, and considering the ease of use and local tolerability of this depot formulation, we believe that the choice among the different schedules has to be individualized based on preference and health-care system

convenience. Arguably, semiannual injections can provide benefits in terms of patient visits and use of resources, but this hypothesis remains to be tested formally in our specific health-care scenario. In Japan, for example, the 6-month formulation was found to reduce medical costs, loss of productivity, and intangible costs in comparison with the 3-month formulation (16). Likewise, in a cost--minimization analysis conducted in Europe, the 6-month formulation was found to offer the greatest cost savings, and the authors considered that it should be the treatment of choice in eligible European patients (17). In the Brazilian health-care system, which aims at providing universal coverage for all citizens (18), it is conceivable that a reduced number of patient visits, especially for the elderly and for those living far from the treatment center, may bring efficiencies and allow for the opening of vacancies for other patients in need.

CONCLUSIONS

Our study confirms that serum PSA levels can be effectively reduced in most of the patients with prostate cancer treated with monthly, quarterly, or semiannual injections of this LHRH agonist. This therapeutic goal is achieved at the expense of a relatively favorable toxicity profile, and it is hoped that schedules of administration every 6 months will bring the added benefit of convenience and cost savings in clinical practice in Brazil and elsewhere.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359-86.
2. Taitt HE. Global Trends and Prostate Cancer: A Review of Incidence, Detection, and Mortality as Influenced by Race, Ethnicity, and Geographic Location. Am J Mens Health. 2018;12:1807-23.
3. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol. 2012;61:1079-92.
4. Sierra MS, Soerjomataram I, Forman D. Prostate cancer burden in Central and South America. Cancer Epidemiol. 2016;44(Suppl 1):S131-S40.
5. Brasil. Ministério da Saúde. Instituto Nacional de Câncer. Informativo Detecção Precoce. Year 8, nr. 2, July/December 2017. Monitoramento das ações de controle do câncer de próstata. Available at. <http://www.saude.df.gov.br/wp-conteudo/uploads/2018/03/Informativo-C%C3%A2ncer-de-Pr%C3%B3stata-2017.pdf> (Accessed 21 December 2018).
6. Merseburger AS, Alcaraz A, von Klot CA. Androgen deprivation therapy as backbone therapy in the management of prostate cancer. Onco Targets Ther. 2016;9:7263-74.
7. Mottet N, Van den Bergh RCN, Briers E, et al. European Association of Urology. Prostate Cancer Guidelines. Available at. <https://uroweb.org/guideline/prostate-cancer/> (Accessed 22 December 2018).
8. Grant JB, Ahmed SR, Shalet SM, Costello CB, Howell A, Blacklock NJ. Testosterone and gonadotrophin profiles in patients on daily or monthly LHRH analogue ICI 118630 (Zoladex) compared with orchiectomy. Br J Urol. 1986;58:539-44.
9. Chu FM, Jayson M, Dineen MK, Perez R, Harkaway R, Tyler RC. A clinical study of 22.5mg. La-2550: A new subcutaneous depot delivery system for leuprolide acetate for the treatment of prostate cancer. J Urol. 2002;168:1199-203.
10. Crawford ED, Sartor O, Chu F, Perez R, Karlin G, Garrett JS. A 12-month clinical study of LA-2585 (45.0 mg): a new 6-month subcutaneous delivery system for leuprolide acetate for the treatment of prostate cancer. J Urol. 2006;175:533-6.
11. Ouzaid I, Rouprêt M. [The role of a 6-month depot form of hormone therapy in the treatment of advanced hormone-dependent prostate cancer: Results from the 'ELIRE' observational study]. Prog Urol. 2011;21:866-74.
12. Tunn UW. A 6-month depot formulation of leuprolide acetate is safe and effective in daily clinical practice: a non-interventional prospective study in 1273 patients. BMC Urol. 2011;11:15.
13. Braeckman J, Michielsen D. Efficacy and tolerability of 1- and 3-month leuprorelin acetate depot formulations (Eligard(®)/ Depo-Eligard(®)) for advanced prostate cancer in daily practice: a Belgian prospective non-interventional study. Arch Med Sci. 2014;10:477-83.

14. Ohlmann CH, Gross-Langenhoff M. Efficacy and Tolerability of Leuprorelin Acetate (Eligard®) in Daily Practice in Germany: Pooled Data from 2 Prospective, Non-Interventional Studies with 3- or 6-Month Depot Formulations in Patients with Advanced Prostate Cancer. Urol Int. 2018;100:66-71.
15. Hupe MC, Hammerer P, Ketz M, Kossack N, Colling C, Merseburger AS. Retrospective Analysis of Patients With Prostate Cancer Initiating GnRH Agonists/Antagonists Therapy Using a German Claims Database: Epidemiological and Patient Outcomes. Front Oncol. 2018;8:543.
16. Goto R, Uda A, Hiroi S, Iwasaki K, Takashima K, Oya M. Cost analysis of leuprorelin acetate in Japanese prostate cancer patients: comparison between 6-month and 3-month depot formulations. J Med Econ. 2017;20:1155-62.
17. Wex J, Sidhu M, Odeyemi I, Abou-Setta AM, Retsa P, Tombal B. Leuprolide acetate 1-, 3- and 6-monthly depot formulations in androgen deprivation therapy for prostate cancer in nine European countries: evidence review and economic evaluation. Clinicoecon Outcomes Res. 2013;5:257-69.
18. Lopes LC, Barberato-Filho S, Costa AC, Osorio-de-Castro CG. Rational use of anticancer drugs and patient lawsuits in the state of São Paulo, Southeastern Brazil. Rev Saude Publica. 2010;44:620-8.

Correspondence address:
Carla Simone Moreira de Freitas, MD, MSc
Hospital do Câncer de Muriaé
Av. Cristiano Ferreira Varella, 555, Universitário
Muriaé, Minas Gerais, 36.880-000, Brasil
Fax: +55 32 3729-7000
E-mail: csmf34438@gmail.com

ORIGINAL ARTICLE

Vol. 46 (3): 390-397, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0230

Comparison of automated irrigation systems using an in vitro ureteroscopy model

Donald Fedrigon III [1], Luay Alshara [1], Manoj Monga [1]

[1] *Cleveland Clinic, Glickman Kidney & Urological Institute, Cleveland, OH, USA*

ABSTRACT

Introduction: Two automated irrigation systems have been released for use during endoscopic procedures such as ureteroscopy: the Cogentix RocaFlow® (CRF) and Thermedx FluidSmart® (TFS). Accurate pressure control using automated systems may help providers maintain irrigation pressures within a safe range while also providing clear visualization. Our objective was to directly compare these systems based on their pressure accuracy, pressure-flow relationships, and fluid heating capabilities in order to help providers better utilize the temperature and pressure settings of each system.

Materials and Methods: An in vitro ureteroscopy model was used for testing, consisting of a short semirigid ureteroscope (6/7, 5F, 31cm Wolf 425612) connected to a continuous digital pressure transducer (Meriam m1550). Each system pressure output and flow-rate, via 100mL beaker filling time, was measured using multiple trials at pressure settings between 30 and 300mmHg. Output fluid temperature was monitored using a digital thermometer (Omega DP25-TH).

Results: The pressure output of both systems exceeded the desired setting across the entire tested range, a difference of 15.7±2.4mmHg for the TFS compared to 5.2±1.5mmHg for the CRF (p <0.0001). Related to this finding, the TFS also had slightly higher flow rates across all trials (7±2mL/min). Temperature testing revealed a similar maximum temperature of 34.0ºC with both systems, however, the TFS peaked after only 8 minutes and started to plateau as early as 4-5 minutes into the test, while the CRF took over 18 minutes to reach a similar peak.

Conclusions: Our in vitro ureteroscopy testing found that the CRF system had better pressure accuracy than the TFS system but with noticeably slower fluid heating capabilities. Each system provided steady irrigation at safe pressures within their expected operating parameters with small differences in performance that should not limit their ability to provide steady irrigation at safe pressures.

ARTICLE INFO

Donald Fedrigon III
http://orcid.org/0000-0001-6752-1829

Keywords:
Research; Technology; Ureteroscopy

Int Braz J Urol. 2020; 46: 390-7

Submitted for publication:
April 08, 2019

Accepted after revision:
August 30, 2019

Published as Ahead of Print:
October 30, 2019

INTRODUCTION

Endoscopic urological procedures require adequate irrigation to ensure clear visualization and efficient stone clearance throughout procedures such as ureteroscopy. Ureteroscopes often require pressurized irrigation since they utilize a small, shared working and irrigation channel, which increases resistance. Adequate irrigation is important for dilation of the ureter and pelvicalyceal system, enhancing instrument passage and visibility.

While pressurized irrigation during endoscopic procedures is often necessary for clear

visualization and efficient stone clearance, its use can also lead to elevated renal pelvis pressures (RPP). This elevation in pressure may cause retrograde flow of fluid, bacteria, and/or endotoxins from the urinary collecting system into the systemic venous circulation, referred to as pyelovenous backflow (1). Therefore, accurate pressure control using automated systems helps providers maintain irrigation pressures within a safe range throughout the procedure.

Various techniques have been used to enhance irrigation, including gravity drainage, pressurized irrigation bags, and handheld or foot activated bulb or syringe-based systems (2). More recently, two automated systems have entered the market to provide digital temperature and pressure monitoring, the Thermedx FluidSmart (TFS) ® and the Cogentix RocaFlow (CRF) ®. Both systems provide continuous irrigation with pressure control and fluid warming.

The Thermedx FluidSmart (TFS) ® system can provide irrigation pressures between 30 and 300mmHg via a rollerball pump. The Cogentix RocaFlow (CRF) ® system can provide pressures up to 735mmHg (1000cmH_2O) via two chambers pressurized with compressed medical air which house the saline bags. Each system's pressure settings is operated via touchscreen and has procedure and specialty specific profiles including transurethral resections, ureteroscopy, and percutaneous nephrolithotomy. The fluid warming system employed by each system is slightly different. The TFS tubing includes a fluid distribution cartridge that slots into a heating unit which warms exiting fluid, which can be set by the user to a maximum of 40ºC. The CRF heats each chamber's respective saline bag, which is preset to 38±2ºC. Both systems have the option to provide suction fluid return as well. The TFS also has a continuous monitoring system to display the current temperature and flow rate as well as to record the fluid usage volume, total fluid deficit, and average temperature.

A previous in vitro analysis of the TFS system was performed at our institution using a rigid ureteroscopy model to characterize the rate of temperature change, pressure accuracy, and the precision of the continuous pressure monitoring (3). This analysis demonstrated that the TFS system overestimated the temperature and flow rate while underestimating the pressure supplied, however, these discrepancies were not significant enough to limit functionality or safety (3). As far as we are aware, no similar in vitro or in vivo comparisons using the Thermedx FluidSmart® or the Cogentix RocaFlow® have been conducted since this publication. The objective of this study was to directly compare both automated systems based on irrigating pressure accuracy, pressure--flow relationships, and fluid heating efficiency in order to help providers better utilize the temperature and pressure settings of each system.

MATERIALS AND METHODS

Pressure and temperature measurements were performed using a continuous digital pressure transmitter (Meriam m1550) and a continuous read digital thermometer (Omega DP25-TH), respectively. Each system was tested using an in vitro ureteroscopy model with a short semirigid ureteroscope (6/7, 5F, 31cm Wolf 425612). For all tests each system was operated combined with the appropriate tubing set and room-temperature 3L saline bags. Tests for pressure and flow rate were repeated at fourteen different pressure settings across the urology relevant range of 30 to 300mmHg. Due to the preset increments in the CRF system increasing by only 6-7mmHg, the tests for pressures for 95, 140, 200, 245, and 260mmHg were run at 97, 142, 202, 247, and 262mmHg respectively. All calculations were done using the exact pressure used for each system but are displayed as equal in the figures for easier comparison (Figure-1).

Pressure Accuracy

Pressure tests were conducted with a one-inch section of suction tubing connecting the pressure sensor and an adjustable biopsy port (Gyrus ACMI), through which the tip of the scope was inserted before tightening to ensure a watertight seal. Both connections were secured with pipe-fitters tape to prevent leakage (Figure-2). Each irrigation system was attached to the scope directly without any intervening stopcocks or Luer locks using the provided fle-

Figure 1 - Left: Cogentix RocaFlow (CRF), Right: Thermedx FluidSmart (TFS).

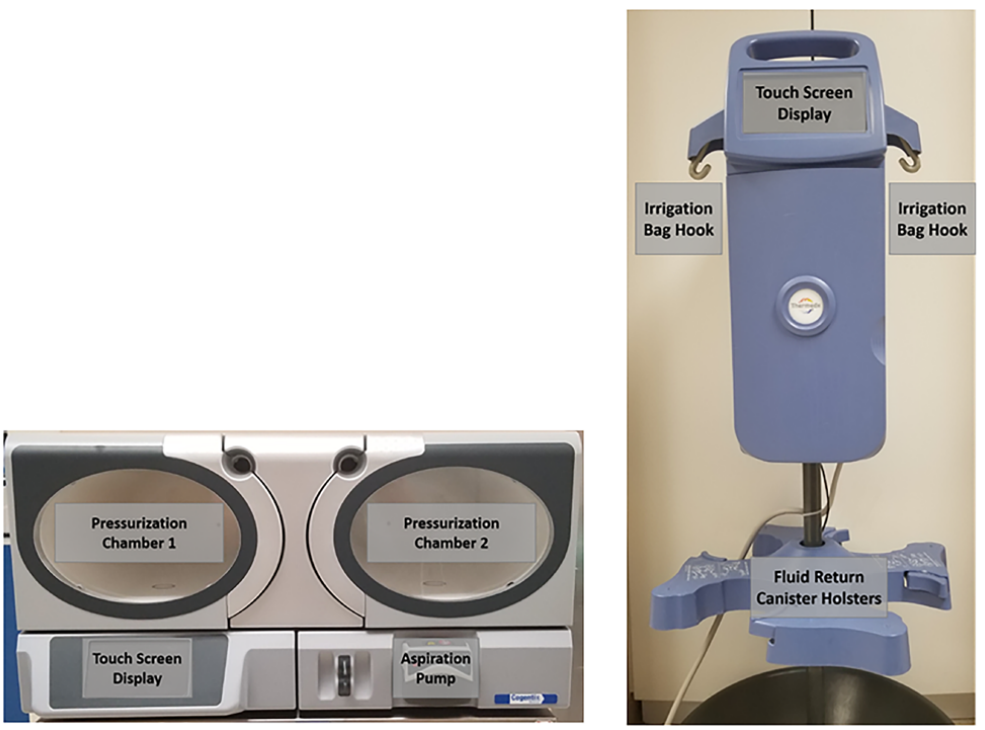
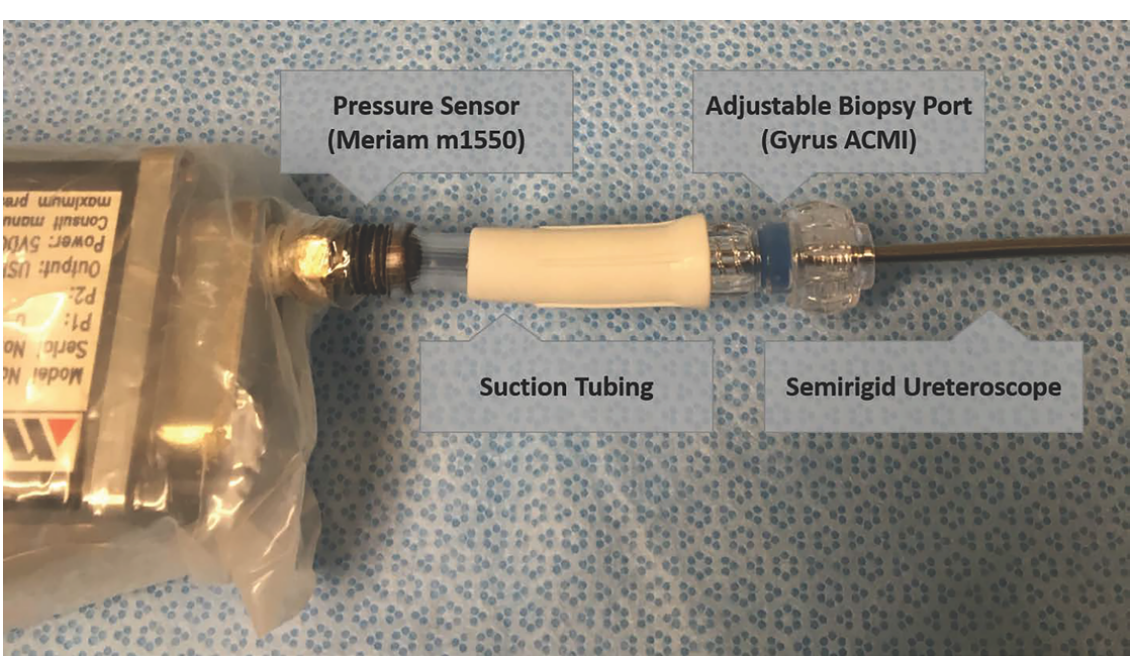


Figure 2 - Pressure testing setup using fluid filled section of tubing attached to the semirigid ureteroscope at one end and the pressure transducer at the other.



xible tubing section for the Rocaflow and the cut end of the Thermedx tubing.

For the TFS, the Thermedx Disposable Ureteroscopy Tubing Set includes a mechanical pressure release valve which is not present in the CRF system. The CRF can be used with both the TURP Tubing Set and Traxerflow Ureteroscopy Tubing Set, with the latter including a hand pump segment with an anti-return valve. In order to maintain consistency neither the TFS pressure release valve or the CRF hand pump sections were used. The pressure sensor and irrigation systems remained level with each other to prevent any gravity influence for both pressure and flow rate tests. Trials were repeated multiple times for each pressure setting and the average used for all calculations.

Flow Rate

Flow rates through the ureteroscope were calculated by recording the time to fill a 100mL beaker at a range of pressure settings. Trials were repeated multiple times for each pressure setting and the average time reported.

Fluid Temperature

The initial fluid temperature, ambient room temperature, and time to maximum temperature were recorded with each system. Ambient room temperature for all tests was between 19.0-20.0ºC and starting fluid temperature was 20.2-20.6ºC unless otherwise noted. Both systems were started from their off state without warmup time and trials were spaced apart to allow each system to cool down between runs. Irrigation fluid temperature was measured with the probe 1cm from the scope tip using standardized flow rates based on the above measurements to provide an equal flow rate for both systems. The TFS system was set to its maximum temperature setting of 40ºC for all tests.

Statistics

Statistical analysis was performed with two-tailed independent t-tests for continuous means. For all tests p-values <0.05 were considered statistically significant. Statistical analysis was performed using R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Pressure Accuracy

For all measured pressures the TFS and CRF systems provided a pressure output above the setpoint set on each system. The TFS demonstrated a pressure difference of 15.7±2.4mmHg compared to 5.2±1.5mmHg for the CRF (mean±SD), this difference in accuracy was statistically significant ($p < 0.0001$, Figure-3). There was no observed trend in pressure output accuracy at the range of pressures tested between 30 and 300mmHg.

Flow Rate

The measured flow rates at each pressure setting for each system are displayed in Figure-4. We observed a slightly higher flow rate from the TFS system, on average 7±2mL/min higher than the CRF systems outputs.

Fluid Temperature

To test the consistency of each system heating mechanism, each system was measured at 136, 164, and 200mL/min flow rates, which did not reveal any consistent differences in rate of temperature increase or maximum temperature. Therefore, the average temperature trend starting from room temperature was reported to provide data generalizable to a variety of usage patterns (Figure-5). The TFS fluid output was heated to above 34.0ºC, close to the maximum of each system after only 8 minutes and started to plateau as early as 4-5 minutes into the test. The CRF system took over 18 minutes to reach the same temperature of 34.0ºC and demonstrated a more gradual temperature slope.

Additionally, we conducted a longer test of the CRF system using two 3L saline bags from room temperature to simulate real-world use when depleting a single bag before switching to the second chamber. During this test the fluid reached a maximum of 35.0ºC at the tail-end of the second bag with a drop from 34.2 to 31.1ºC following the transition between the bags. The average temperature throughout the 48-minute test was 30.8ºC (Figure-6).

Figure 3 - Difference between observed fluid pressure output and set pressure at each pressure increment. Multiple trials repeated at each pressure setting with average displayed.

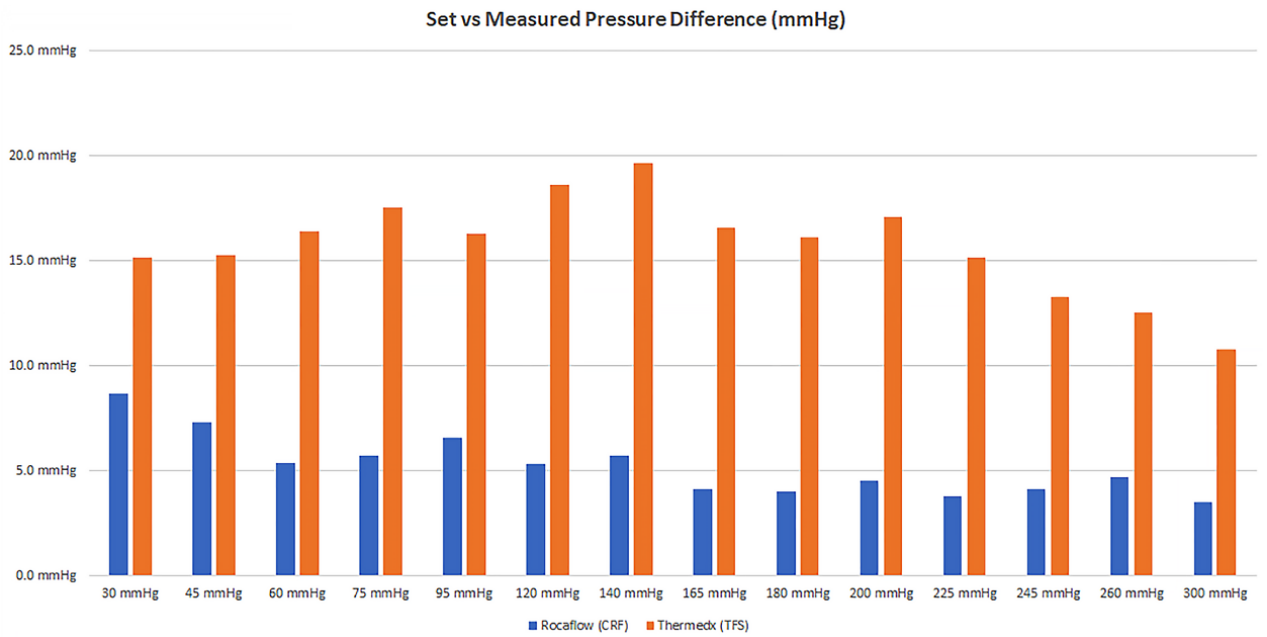


Figure 4 - Observed flow rates as measured by time to fill 100 mL beaker, average time of multiple trials displayed.

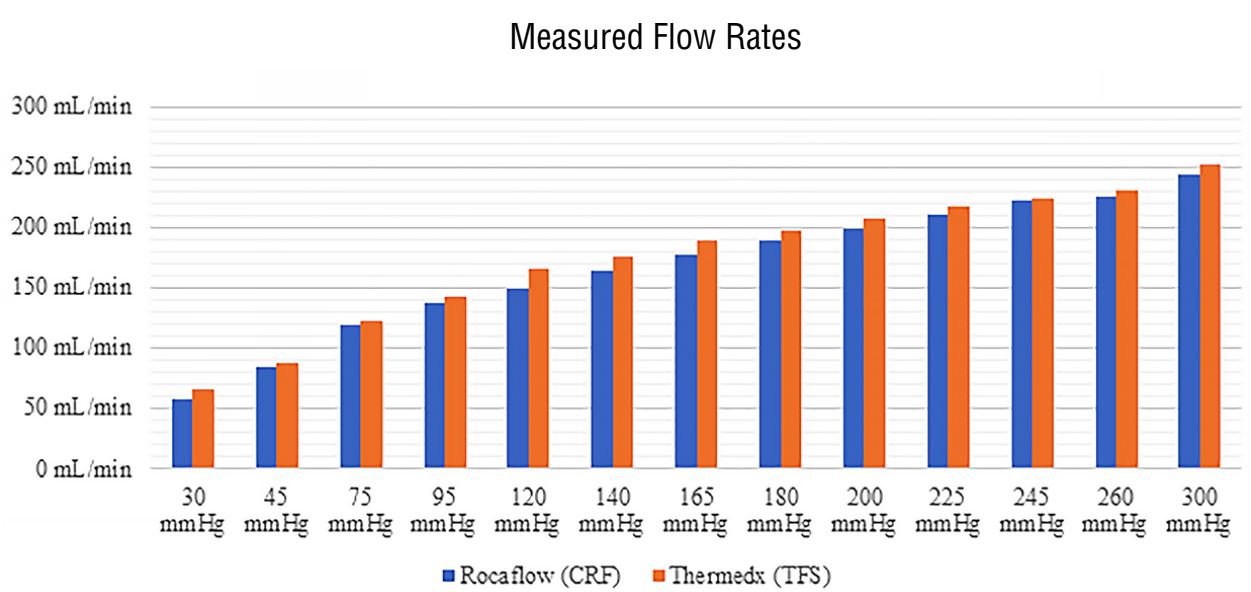


Figure 5 - Temperature of irrigation fluid as measured 1 cm from the scope tip.

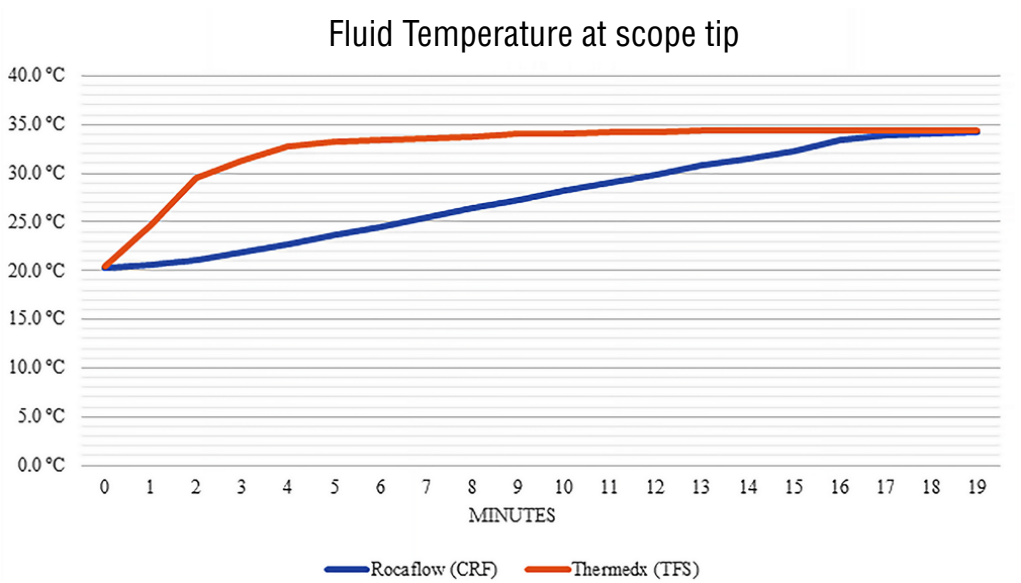
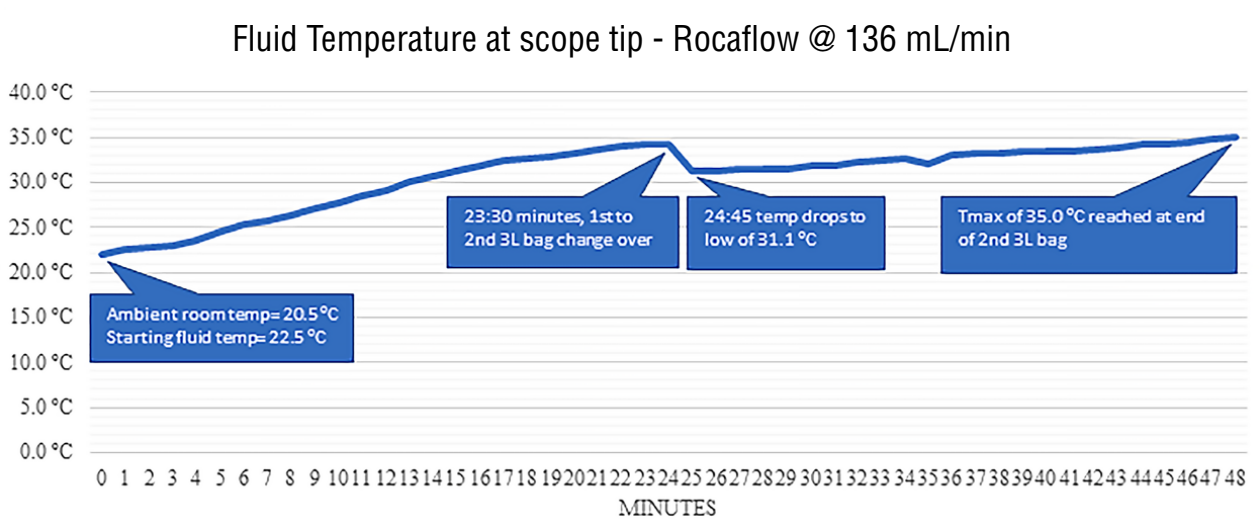


Figure 6 - Temperature at scope tip during full length test of two 3L saline bags.



DISCUSSION

Both the TFS and CRF are automated irrigation systems with pressure and temperature control for the purpose of providing steady irrigation during ureteroscopy. In our previous study evaluating only the Thermedx system, we found that the TFS monitoring system underestimated pressures and overestimated both flow rates and temperatures delivered through the endoscope (3). In this study, we retested both the TFS with the addition of the CRF system, with a focus on pressure accuracy.

Pressure Accuracy

During our testing both systems overestimated the pressure output. However, of the two automated systems the CRF showed better pressu-

re accuracy than the TFS, based on absolute difference between the set and measured pressures.

Gravity based systems and pressurized bag sleeves may cause fluctuations in the output pressure since they cannot account for changes in resistance within the working channel or at the scope tip. The new automated systems aim to address this by monitoring the fluid pressure and adjusting their output to maintain a steady output pressure. These improvements aim to improve visualization, provide a larger working space, and allowing easier progression of instruments in the hope of reducing operative times and improving stone free rates. Lechevallier et al. showed significant reduction in the mean operative time among patients randomized to an automated pressurized irrigation system compared to standard pressurized irrigation, 32% with the rigid instrument and 53% with the flexible instrument, which the authors attributed to the improved working space and visibility (4).

Pressure accuracy is also important for preventing the retrograde flow of fluid, bacteria, and/or endotoxins from the urinary collecting system into the systemic venous circulation, referred to as pyelovenous or pyelolymphatic backflow, commonly believed to occur at pressures greater than 30mmHg. Previous literature estimates that the fluid absorption from pressures in excess of this threshold during ureteroscopy is fairly limited compared to percutaneous nephrolithotomy (1, 5). Since both automated irrigation systems are intended for use during both procedures, our pressure accuracy analysis is likely relevant to both procedures. These systems may provide better control to minimize any unwanted increase in pressures above the threshold without compromising visibility and operative time.

Flow Rate

We observed slightly higher flow rates for the TFS system across all tested pressures, which may be a by-product of the higher-pressure output of this system. Subjectively, we also observed during our flow testing that the CRF system demonstrated a slightly less variable flow, similar to what would be expected from passive gravity irrigation.

Most irrigation systems in use today utilize either passive gravity-driven flow or active irrigation provided by hand or foot-operated pumps. For pump operated systems, flow rate fluctuations may cause more erratic movement of stone fragments. Gravity based systems on the other hand, may exert less force than active irrigation systems (6). Minimizing stone migration during ureteroscopy by providing a more tempered, steadier flow while also maintaining adequate force via an automated system would therefore be expected to correlate with reduced operative times.

Proper irrigation is important not only for minimizing stone migration and renal pelvis pressures but also for proper temperature control during laser lithotripsy. A recent in vitro analysis by Wollin et al. found that while adequate irrigation can maintain stable temperatures across a range of laser settings, decreasing irrigation rates can result in potentially dangerous temperature elevations even with low power laser use (7). An ex vivo model used by Molina et al. observed that irrigation decreased external ureteral temperature elevations during laser lithotripsy (8).

Fluid Temperature

While both systems eventually reached a similar maximum temperature of 35ºC, still below the advertised temperature set point for both systems, the CRF system took much longer to reach this maximum. This appears to be a reflection of the different approaches to fluid warming used by each system. The CRF heats the entire bag within the chamber and therefore showed a steady rise throughout the test, with the maximum only being achieved when a small amount of fluid remained in the bag to be heated. The additional time to heat more fluid was also observed in our longer trial showing a temperature dip when switching to a full bag that had been heating in the second chamber. The TFS system meanwhile, heats only the small amount of fluid exiting the machine and therefore reached its maximum temperature in a much shorter period as the internal heating element warms to the proper temperature.

The usage of room temperature instead of warmed irrigation fluids during some endourological procedures such as percutaneous nephrolithotomy has been associated with significant decreases in body temperature as well as longer anesthesia recovery times (9). Additionally, mild perioperative hypothermia has been associated with adverse events such as increased blood loss, weakened immune responses, and discharge times (10). Therefore, having an efficient heating component during these high volume procedures may have a noticeable impact on patient outcomes.

This study is limited by its in vitro nature since the irrigation systems characteristics and measurements may be affected by the physiological properties of a real kidney and urological system. Additionally, in order to maintain consistency between the two irrigation systems tubing we excluded some elements that could affect pressures such as release valves and hand-pump segments. Future in vivo studies may help confirm their clinical applicability and cost in order to help providers better understand the operating characteristics during the use of these systems.

CONCLUSIONS

When comparing automated irrigation systems using an in vitro ureteroscopy model the Cogentix RocaFlow (CRF) ® system demonstrated more accurate pressure output compared to the Thermedx FluidSmart (TFS) ® system. While both systems reached a similar peak temperature output, the CRF system showed noticeably slower heating capabilities. Despite these differences in operating characteristics both systems performed within their expected parameters, with small variations that should not limit their ability to provide steady irrigation at safe pressures.

ABBREVIATIONS

CRF = Cogentix RocaFlow
mmHg = Millimeter of mercury
SD = Standard deviation
TFS = Thermedx FluidSmart

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Kukreja RA, Desai MR, Sabnis RB, Patel SH. Fluid absorption during percutaneous nephrolithotomy: does it matter? J Endourol. 2002;16:221-4.
2. Blew BD, Dagnone AJ, Pace KT, Honey RJ. Comparison of Peditrol irrigation device and common methods of irrigation. J Endourol. 2005;19:562-5.
3. De S, Torricelli FC, Sarkissian C, Kartha G, Monga M. Evaluating the automated Thermedx Fluid Management System in a ureteroscopy model. J Endourol. 2014;28:549-53.
4. Lechevallier E, Luciani M, Nahon O, Lay F, Coulange C. Transurethral ureterorenolithotripsy using new automated irrigation/suction system controlling pressure and flow compared with standard irrigation: a randomized pilot study. J Endourol. 2003;17:97-101.
5. Cybulski P, Honey RJ, Pace K. Fluid absorption during ureterorenoscopy. J Endourol. 2004;18:739-42.
6. Hendlin K, Weiland D, Monga M. Impact of irrigation systems on stone migration. J Endourol. 2008;22:453-8.
7. Wollin DA, Carlos EC, Tom WR, Simmons WN, Preminger GM, Lipkin ME. Effect of Laser Settings and Irrigation Rates on Ureteral Temperature During Holmium Laser Lithotripsy, an In Vitro Model. J Endourol. 2018;32:59-63.
8. Assimos DG. Re: Long-term urine biobanking: storage stability of clinical chemical parameters under moderate freezing conditions without use of preservatives. J Urol. 2015;193:898.
9. Tekgul ZT, Pektas S, Yildirim U, Karaman Y, Cakmak M, Ozkarakas H, et al. A prospective randomized double-blind study on the effects of the temperature of irrigation solutions on thermoregulation and postoperative complications in percutaneous nephrolithotomy. J Anesth. 2015;29:165-9.
10. Reynolds L, Beckmann J, Kurz A. Perioperative complications of hypothermia. Best Pract Res Clin Anaesthesiol. 2008;22:645-57.

Correspondence address:
Manoj Monga, MD
Cleveland Clinic-Glickman Urological & Kidney Institute
9500 Euclid Avenue, Cleveland, OH 44195, USA
Telephone: +1 216 445-8678
E-mail: mongam@ccf.org

EDITORIAL COMMENT

Vol. 46 (3): 398-399, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0230.1

Editorial Comment: Comparison of automated irrigation systems using an in vitro ureteroscopy model

Bruno Marroig [1]

[1] *Departamento de Cirurgia Geral, Universidade do Estado do Rio de Janeiro - UERJ, Rio de Janeiro, RJ, Brasil*

COMMENT

Several automated irrigation systems have been developed at least along the last three decades. In 1996, Sakhadeo et al. reported a new system of irrigation for ureteroscopy and recommended more widespread use of it by urologists (1). Another automated irrigation system controlling pressure and flow showed consistent reduction in mean ureteroscopy time (32% less with a semi-rigid ureteroscope and 53% less with a flexible instrument), probably due to a wider working space and higher improved visibility, allowing easier progression and manipulation of instruments (2). Some devices control pressure flow output and temperature of saline irrigation.

The problem of elevated intrarenal pressure (IRP) is pyelovenous backflow of fluids, bacteria and/or endotoxins. The safest irrigation method used during ureteroscopy is by gravity, but it is usually insufficient to overcome liquid resistance in a narrow endoscope, especially if there is any instrument inside the working/irrigation channel. Pressurized irrigation bags routinely used, with or without pump systems, may lead to a wide range of intrarenal pressures, reported from 8.27 to 199.35 cm H2O, depending on the irrigation pressure applied (3). In order to achieve better ureteroscope visualization or allow its progression across ureter, pump flush may lead to increased flow and IRP, which can cause ureteral stone push up. Some devices, such as ureteral access sheath and automated infusion/pressure control devices, may influence intrarenal pressure. In general, IRP remains lower than 30 cm H2O when ureteral access sheath is used because it functions as a escape valve, thereby stabilizing the IRP. Similarly, automated infusion/pressure control devices maintain pre-setting IRP with an automated irrigation/suction pump system (3).

The well conducted study by Fedrigon III and collegues (4) makes a comparison between two automated irrigation systems using an in vitro ureteroscopy model. They first analyzed pressure accuracy. The authors showed that both systems overestimated output pressure, which is not necessarily "bad news". Although poor accuracy may seem disadvantageous at first sight, at least pressure is overestimated. It would be dangerous for the patient if pressure was underestimated, rendering patients vulnerable to the consequences of elevated IRP. With this piece of information, surgeons can decide if they pre-set higher IRP, if necessary, according to the patient's clinical presentation. Automated systems often need more attention, as advised by Butticè and collegues (5). They call for caution when using the Roboflex Avicenna pump, particularly at high speed settings with resulting high-pressure irrigation during flexible ureteroscopy. This means that even with automated systems, high IRP may occur.

They next investigated flow rate. They found slightly higher flow rate for TFS system, while CRF demonstrated a slightly less variable flow, similar to what would be expected from passive gravity irrigation. The minimal irrigation pressure needed to provide an adequate visualization and good instru-

mentation should be used to mitigate stone migration. An adequate flow rate is notably important in any urologist understanding, but an important issue not usually considered by surgeons is that adequate flow rates help controlling proper temperature during laser lithotripsy. In 2014 Molina and collegues (6) evaluated the temperature profile of laser litithotripsy in two urinary tract *ex vivo* models in *Ovis aries*. Thermography studies found an important increase in wall temperatures of the urothelium and external ureteral during laser activation. Even in all different testing situations, an important conclusion was that temperature increase was significantly higher with non-irrigation. With irrigation, temperature increase is not sufficient to cause any harm to kidney cells (6). More recently, Butticè et al. published a similar conclusion (7).

Irrigation is needed most of the time during ureteroscopy, but attention should be paid when instrument working channel is occupied with a thicker laser fiber or even with a thinner one, but with a basket in it at the same time (8). The space left for irrigation may lead to a very reduced flow rate and increased intrarenal temperature during laser activation (9). In cases where automated irrigation system is used, activation of laser fiber leads to a rapid increase in temperature, especially in heated saline (10). Even with continuous flow, attention is needed because elevated temperature inside renal cavity causes tissue damage. While experienced surgeons may take advantages of such systems, caution is recommended to those surgeons who are not familiar with them.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sakhadeo NB, Venkatesh R, Trafford P, Parr NJ. A new system of irrigation for ureteroscopy. Br J Urol. 1996;78:639-40.
2. Lechevallier E, Luciani M, Nahon O, Lay F, Coulange C. Transurethral ureterorenolithotripsy using new automated irrigation/suction system controlling pressure and flow compared with standard irrigation: a randomized pilot study. J Endourol. 2003;17:97-101.
3. Tokas T, Skolarikos A, Herrmann TRW, Nagele U; Training and Research in Urological Surgery and Technology (T.R.U.S.T.)-Group. Pressure matters 2: intrarenal pressure ranges during upper-tract endourological procedures. World J Urol. 2019;37:133-42.
4. Fedrigon D III, Alshara L, Monga M. Comparison of automated irrigation systems using an in vitro ureteroscopy model. Int Braz J Urol. 2020;46:390-7.
5. Butticè S, Proietti S, Dragos L, Traxer O. Are You Familiar with the Flow of the Roboflex Avicenna Pump? Allow Me to Explain. J Endourol. 2017;31:418-9.
6. Molina WR, Silva IN, Donalisio da Silva R, Gustafson D, Sehrt D, Kim FJ. Influence of saline on temperature profile of laser lithotripsy activation. J Endourol. 2015;29:235-9.
7. Butticè S, Sener TE, Proietti S, Dragos L, Tefik T, Doizi S, Traxer O. Temperature Changes Inside the Kidney: What Happens During Holmium:Yttrium-Aluminium-Garnet Laser Usage? J Endourol. 2016;30:574-9.
8. Patel N, Monga M. Ureteral access sheaths: a comprehensive comparison of physical and mechanical properties. Int Braz J Urol. 2018;44:524-35.
9. Yoo J, Lee SJ, Choe HS, Kim HY, Lee JH, Lee DS. Anterograde irrigation - assisted ureteroscopic lithotripsy in patients with percutaneous nephrostomy. Int Braz J Urol. 2019;45:406-7.
10. Bach T, Geavlete B, Herrmann TR, Gross AJ. Working tools in flexible ureterorenoscopy--influence on flow and deflection: what does matter? J Endourol. 2008;22:1639-43.

ARTICLE INFO

Bruno Marroig
https://orcid.org/0000-0002-9522-5709

Int Braz J Urol. 2020; 46: 398-9

Submitted for publication:
January 25, 2020

Accepted after revision:
February 10, 2020

Bruno Marroig, MD

Departamento de Cirurgia Geral
Universidade do Estado do Rio de Janeiro - UERJ, Rio de Janeiro
Av. Prof. Manuel de Abreu, 444 - 2º andar.
Vila Isabel. Rio de Janeiro, RJ, 20550-170, Brasil
E-mail: urologiarj@gmail.com

ORIGINAL ARTICLE

Vol. 46 (3): 400-408, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0363

Current scenario of endourological treatment of kidney stones in brazil: results of a national survey

Rafael Haddad Astolfi [1], Raphael Carrera [1], Nelson Gattas [2], Ricardo Bertolla [3], Fabio Sepulveda [4], Ernesto Reggio [5], Alex Elton Meller [1]

[1] Disciplina de Urologia, Universidade Federal de São Paulo – UNIFESP, São Paulo, SP, Brasil; [2] Escola Paulista de Medicina - UNIFESP, São Paulo, SP, Brasil; [3] Departamento de Cirurgia, Divisão de Urologia, Seção de Reprodução Humana Universidade Federal de São Paulo – UNIFESP, São Paulo, SP, Brasil; [4] Disciplina de Urologia, Universidade Estadual do Sudoeste da Bahia - UESB, Vitória da Conquista, BA, Brasil; [5] Uroclínica de Joinville, Joinville, SC, Brasil

ABSTRACT

Objective: To elucidate the current scenario of endourology in Brazil for the treatment of urinary lithiasis, with an emphasis on regional differences and the reasons why certain techniques are still underutilized.
Materials and Methods: An electronic questionnaire was sent by email to the 4,745 members of the Brazilian Urological Society (BSU) in 2016 to collect information on the 3 main endourological procedures used in the treatment of nephrolithiasis: Semi-rigid ureteroscopy (URS), Flexible ureteroscopy (F-URS) and percutaneous nephrolithotripsy (PCNL).
Results: A total of 1,267 urologists answered the questionnaire. It was observed that the vast majority perform URS (95.6%), while 80.2% perform F-URS and only 72.1% perform PCNL. Regarding the surgical volume, most perform up to 10 procedures per month (73.4% to 88.2%) and the main impediment was the lack of patients with the pathology (42.1% to 67.7%). The lack of equipment or hospital infrastructure was one of the main limiting factors for rigid (23%) and flexible (38.1%) URS, mainly in the North and Northeast regions of the country. Regarding PCNL, most of them reported lack of practical experience in the method (29.9%). Finally, most urologists expressed interest in taking courses in endourology.
Conclusion: Ureteroscopy, rigid or flexible, is already well established in the country, requiring the direction of more resources for its practice, especially in less developed regions. Regarding PCNL a significant part of Brazilian urologists still lack practical experience in this procedure, emphasizing the need for greater investment in teaching this technique.

ARTICLE INFO

Rafael Astolfi
http://orcid.org/0000-0003-1531-7863

Keywords:
Kidney Calculi; Epidemiology; Ureteroscopy; Therapeutics

Int Braz J Urol. 2020; 46: 400-8

Submitted for publication:
June 11, 2019

Accepted after revision:
September 04, 2019

Published as Ahead of Print:
December 30, 2019

INTRODUCTION

Nephrolithiasis is one of the most frequent urological diseases, with a significant burden on public health system and on patient's quality of life. Its global prevalence has increased over the years, from 2 to 20% depending on the geographical region, being higher in developed countries (1-3). In the USA, more than 8.8% of the population is affected by the disease (4), with an annual cost

of up to 5.3 billion dollars, including direct costs of treatment and indirect secondary costs due to loss of work productivity (5), since kidney stones affect in particularly active economic people (6). In Brazil, according to DATASUS, 52 million reais (approximately US$ 13 million) have been spent in 2017 to treat kidney stones (7).

Over the last 30 years, treatment changed profoundly due to technological advances in minimally invasive techniques, that almost completely replaced open surgeris (1, 8, 9). The development of digital endoscopes and improvements of Holmium:Yag lasers and hydrophilic and flexible devices mande endourological procedures safer and more efficient, reducing surgical morbidity while improving clinical results (10, 11). In line with this world tendency, in the last 15 years, the number of endoscopic procedures increased greatly in Brazil, probably due to better training of young urologists during residency and to a higher availability of endoscopic equipment in different health centers (12).

The objective of this study was to clarify the current use of endourology on the treatment of kidney stones in Brazil, including regional differences and the reasons why some techniques are still underutilized. This information will aid the development of continuous education programs proposed by the Brazilian Urological Society (BSU), the improvement of endourology teaching in medical residency programs and better planning of resources distribution in different urological services in Brazil.

MATERIAL AND METHODS

Demographic data colection

Many sources were utilized to gather our data bank. After permission of the Brazilian Urological Society (BSU) to access its data, we have evaluated the total number of Brazilian members in debt or not, as well as the number of members of each Brazilian macro-region (North, Northeast, South, Southeast, Center-West). We have also evaluated the number of medical residency programs in Urology acredited by BSU in total and in each region. In order to estimate the number of urologists practicing in Brazil (members and non-members of BSU) we obtained data from the Federal Board of Medicine (13).The National Board of Medical Residencies (Conselho Nacional de Residências Médicas - CNRM) provided the number of residency programs in urology, accredited or not by BSU, in total and in each Brazilian region. All information referred to 2018. In relation to general epidemiological characteristics, the databank of Instituto Brasileiro de Geografia e Estatística (IBGE - Brazilian Institute of Geography and Statistics) to determine the number of inhabitants in Brazil and the value of the Gross Internal Product (GPI) in total and according to the different regions. Finally, the HDI (Human Development Index) total and divided were obtaines from the databank of IPEA-Instituto de Pesquisa Econômica Aplicada-Institute of Applied Economics Research-of 2016 (14).

Research instrument

From January to September, 2016, a national survey was proposed by BSU to evaluate the current status of endourology in Brazil. An electronic questionnaire of 12 items (multiple choice) was sent by e-mail to all 4.745 current BSU members to collect demographic information and the practice of the three most used endourological procedures to treat kidney stones: semi-rigid ureteroscopy (URS), flexible ureteroscopy (F-URS), and percutaneous nephrolithotomy (PCNL). It was also asked to the respondents to estimate monthly number of each procedure and where he/she was located according to each of the five Brazilian regions (North, Northeast, South, Southeast and Center-West). Monthly rate of procedures was divided into three categories according to answer: <10 patients/month, 10-20 patients/month and >20 patients/month. If the respondents did not perform the procedure or considered the number insufficient, they were asked to point the reason why:1) Lack of equipment/hospital infrastructure; 2) Lack of theoretical knowledge of the method; 3) Lack of practical experience with the technique; 4) Lack of trained support staff; or 5) lack of patients with the disease. Finally, the respondents were asked to inform if they would participate in theoretical-practical courses ministered by experts in their regions, as well as which distance

would they be willing to travel to participate (<50 km, 50-200 km, or >200 km). The answers were automatically and anonymously distributed in a database under confidentiality of the researcher (A.M.).

Statistical analysis

Statistical analysis was made by SPSS 17.0 software for Windows. Descriptive analysis was performed for continuous and categoric variables. When appropriate, frequencies were compared among groups using the Chi-Square test and, in that case, the maximum alpha error was set at 5%.

RESULTS

General data of urology in brazil

In 2018, 5.328 urologists were practicing in Brazil, 97.8% male and 2.2% female, with a median age of 48.7 years, representing 1.4% of the total of Brazilian medical doctors. Urologists were distributed unevenly in the Brazilian territory and were concentrated mainly in the Southeast region (52.2%) and in lesser number in the North region (4.3%). Among all Brazilian urologists, most were members of BSU (98.5%) and with lower frequency in the Center-West region (52.3%). In relation to the number of medical residency programs in urology (MRU), in 2018 there were 122 programs in Brazil, with a total of 142 positions per year, most located in the Southeast (57.4%) and with the lowest presence in the North region (4.1%). Among all, 80 MRU were accredited by BSU (65.6%) and in South and Center-West it was observed a higher proportion of accreditation according to total number (80% and 70%, respectively). BSU accreditation ensures the presence of training in all modalities of treatment of urinary lithiasis. In relation to the number of programs that offered fellowships in endourology (Internship and Improvement Programs) only 3 were accredited by BSU, 1 in South region (Santa Catarina State) and 2 in Southeast (in São Paulo State). Finally, in relation to the number of urologists/inhabit- ants, Southeast region presented the higher pro- portion (1: 31, 745 inhabitants), and the North and Northeast region had the lowest number of professionals (1: 90.095 and 1: 70.771 inhabitants, respectively). All data are presented in detail in Table-1.

Current status of endourology in Brazil

A total of 1.267 urologists answered the questionnaire, corresponding to 26.7% of all members of BSU (5.328). Among the respondents, 53.3% lived in the Southeast region (674), 17.9% in South region (227), 15.4% in Northeast (195), 8.5% in Center-West (107) and 4.9% in the North region (62). The percentage of BSU members per

Table 1 - Urology Demographic Data in Brazil.

	South	Southeast	Center-west	Northeast	North	Total
Total number of urologists	900 (16.9%)	2.781 (52.2%)	533 (10%)	879 (16.5%)	229 (4.3%)	5.328
Urologists members OF BSU	737 (15.5%)	2.739 (57.5%)	279 (5.9%)	809 (17.3%)	181 (3.8%)	4.745
BSU urologists/Total	81.9%	98.5%	52.3%	92%	79%	89.1%
Total number OF MRU	15 (12.3%)	70 (57.4%)	10 (8.2%)	22 (18%)	5 (4.1%)	122
BSU Accredited MRU	12 (15%)	47 (58.7%)	7 (8.8%)	13 (16.2%)	1 (1.3%)	80
BSU MRU/Total	80%	67.1%	70%	59.1%	20%	65.6%
Urologists/Inhabitants	1: 40.223	1: 31.745	1: 56.903	1: 70.771	1: 99.095	

MRU = Medical Residence in Urology; **BSU** = Brazilian Society of Urology

region that answered questionnaire was 24.6% in the Southeast, 26.4% in the North, 30.8% in the South, 38.3% in the Center-West and 34% in the Northeast.

In general, most urologists perform the three most important endourological procedures for the treatment of kidney stones, especially URS (95.6%), while 80.2% perform F-URS and 72.1% PCNL. In relation to number of procedures, the majority of urologist perform 0-10 endourological procedures/month (73.4% to 88.2%), and F-URS was the least performed (11.7% of >10 procedures/month). In relation to the reasons for a low number of procedures or for not performing the technique, most informed that there was a lack of patients with the disease (42.1% to 67.7%). When lack of patients was excluded as a determinant factor, lack of equipment or adequate hospital infrastructure was the main reason for URS (23%) and F-URS (38.1%), while for PCNL the lack of practical experience was the main reason (29.9%).

Finally, most urologists expressed interest in participating in hands-on endourological courses in their region (72%) and most would travel more than 50 km to attend them (73.5%). Likewise, many respondents (42.9%) would travel more than 200 km to participate in these events.

Regional characteristics of endourology in Brazil

The answers of this research were analyzed and compared among different regions in Brazil and data are presented in Table-2.

When we analyze the practice of URS by region, no statistical difference was found in the percentage of urologists that perform the technique (95.3-95.7%, p 0.953); however, when we analyzed the frequency of procedures according to region, there was a higher proportion of urologists from Southeast that performed >20 procedures/month (8.3% vs. 1.7-2.8% p 0.001). In all regions, the main reason for not performing URS was the lack of patients (48.6%-77.3%), however, there was a higher percentage of lack of equipment/hospital infrastructure in North and Northeastern regions when compared to the others, although not significantly different (40% and 31.5% respectively vs. 13.6-26.3%, p=0.069).

In relation to F-URS, the percentage of urologists that performed the technique was significantly higher in the Southeast and North regions that in Northeast, South and Center-West (85.9% and 80.6% vs. 73.8%, 72.7% e 71% respectively, p <0.001). In all regions, there was a predominance of <10 procedures/month (86.2%-92%), while in Center-West there was a significantly higher percentage of urologists performing >20 procedures/month (6.4% vs. 0-2.4%, p 0.028). In relation to the main reason for a lack or low number of procedures, lack of patients predominated only in the Southeast region (52.8% vs. 33.3-41%), while in all other regions the lack of equipment/hospital infrastructure (42-51.2%) was the most important factor, although there was only a statistical significant difference between the Southeast and South regions (p=0.011).

In relation to PCNL according to Brazilian region, there was a statistical significant difference between the rate of urologists that claimed to frequently perform this procedure, with a prevalence in the South region (higher number) and lowest frequency in the Center-West region (82.4% and 48.6% respectively vs 67.7-73.7%, p <0.001). In relation to the number of procedures, there was no significant difference among the different regions, most stating that performed <10 procedures/ month (77% to 80.7%, p 0.642). The main reason for this low number of PCNLs was lack of patients particularly in South and Southeast regions (57% and 47.7%), lack of equipment/hospital infrastructure mainly in North and Northeast region (40% and 32%) and the lack of practical experience in the Center-West region (34.2%). Surprisingly, except in the South region, in all other regions there were many urologists pointing the lack of experience with the technique as one of the main reasons for not performing PCNL (13.2% vs. 32-34.2%, p <0.001). In Center-West and Northeast regions, there was also a higher proportion of urologists that referred lack of theoretical knowledge of the procedure (6.3% and 3.1% respectively vs. 0-1.1%, p <0.001).

Finally, when the respondents were questioned about practical courses of endourology, in all regions there was a higher proportion of interested urologists (67.3-72.5%, p 0.86). In relation to the distance that they would travel to attend

Table 2 - Answers of Respondents.

	Southeast	Northeast	South	CenteR-west	North	P
Do you perform rigid ureterolithotripsy?						**0.953**
Yes	95.7%	95.9%	95.6%	95.3%	95.3%	
How often do you perform r-ult?	**a**	**b**	**b**	**b**	**a, b**	**0.001**
0 to 10	68.5%	78.9%	77.8%	79.6%	82.8%	
10 to 20	23.2%	18.3%	19.9%	18.4%	15.5%	
>20	8.3%	2.8%	2.3%	1.9%	1.7%	
Reason for low use of rigid ult						**0.069**
1 Lack of equipment/ infrastructure of my hospital	17.6%	31.5%	26.3%	13.6%	40%	
2 Lack of patients with the disease	73%	56.2%	68.4%	77.3%	48.6%	
3 Lack of practical experience with the technique	7.7%	7.9%	4.2%	9.1%	8.6%	
4 Lack of theoretical knowledge of the technique	0.5%	0%	0%	0%	0%	
5 Lack of trained support staff (assistants, nurses, etc.)	1.4%	4.5%	1.1%	0%	2.9%	
Do you perform flex-ult?	**a**	**b**	b	**b**	**a, b**	**<0.001**
Yes	85.9%	73.8%	72.7%	71%	80.6%	
How often do you perform flex-ult?	**a**	**a**	**a**	**b**	**a, b**	**0.028**
0 a 10	86.2%	88.9%	92.6%	89.7%	92%	
10 a 20	11.4%	9.7%	6.9%	3.8%	8%	
>20	2.4%	1.4%	0.6%	6.4%	0%	
Reason for low number of flex-ult?	**a**	**a, b**	**b**	**a, b**	**a, b**	**0.011**
1 Lack of equipment/ infrastructure of my hospital	29.3%	42%	51.2%	44.3%	47.5%	
2 Lack of patients with the disease	52.8%	37.5%	33.3%	41%	37.5%	

3 Lack of practical experience with the technique	15.9%	17%	14%	14.8%	12.5%	
4 Lack of theoretical knowledge of the technique	1.4%	2.7%	0%	0%	0%	
5 Lack of trained support staff (assistants, nurses, etc.)	0.7%	0.9%	1.6%	0%	2.5%	
Do you perform PNL?	**a**	**a**	**b**	**c**	**a**	**<0.001**
Yes	73.7%	69.1%	82.4%	48.6%	67.7%	
How often do you perform PNL?						**0.642**
0 to 10	77%	80.3%	80.7%	79.6%	79.5%	
10 to 20	21%	19.7%	16.6%	18.5%	20.5%	
>20	2%	0% [a]	2.7%	1.9%	0%	
Reason for low number of PNL?	**a**	**b**	**c**	**b**	**b**	**<0.001**
1 Lack of equipment/ infrastructure of my hospital	16.2%	32%	25.6%	26.6%	40%	
2 Lack of patients with the disease	47.7%	29.7%	57%	31.6%	24.4%	
3 Lack of practical experience with the technique	33.2%	32%	13.2%	34.2%	33.3%	
4 Lack of theoretical knowledge of the technique	1.1%	3.1%	0.8%	6.3%	0%	
5 Lack of trained support staff (assistants, nurses, etc.)	1.7%	3.1%	3.3%	1.3%	2.2%	
Would you participare in courses in your region?						**0.860**
Yes	72.5%	73.3%	72.2%	67.3%	71%	
Which distance would you travel?	**a**	**b**	**c**	**b**	**d**	**<0.001**
1 - 0-50 Km	33.1%	17.4%	22.7%	19%	14.5%	
2 - 50 - 200 Km	35.6%	23.7%	34.1%	21%	4.8%	
3 - > 200 Km	31.3%	58.9%	43.3%	60%	80.6%	

Rigid ULT = semi-rigid ureterolothotripsy; **Flex-ULT** = flexible ureterolithotripsy; **PNL** = percutaneous nephrolithotomy

*Equal letters inside the same line represent absence of significant statistical difference.

them, there was a statistical significant different ($p < 0.001$) between those who would travel large distances (>200 km), as the Southeast region presented the lowest rate (31.3%), followed by the South Region (43.3%), while the urologists from the North region were those with higher rate of interest (80.6%).

DISCUSSION

In Brazil and Worldwide, the prevalence of nephrolithiasis has increased over the years in the last decades, with a major impact on public health systems (1-5). This increase has been accompanied by the growing use of surgical treatments for kidney stones in developed and underdeveloped countries (9, 12, 15, 16), increasing the importance of a better understanding of the current practices of endourology. Our study has investigated the three most important surgical techniques used for the treatment of nephrolithiasis among Brazilian urologists. To our knowledge, this is the first study to specifically address the demography of endourology in Brazil.

After reviewing the answers of the question forms, it was possible to conclude that URS, rigid or flexible, is well established in Brazil, since more than 80% of the respondents claimed to perform this procedure in their daily practice, regardless of their region. However, PCNL is still less performed by Brazilian urologists (72%) in comparison to ureteroscopy, probably due to its higher complexity and the risk of more severe complications, such as sepsis, injury of adjacent organs, hemorrhage and death, therefore generally being reserved for more complex cases. The fact that lack of patients corresponds to the main reason why most urologists perform <10 surgeries/month suggests that, in Brazil, endourology is decentralized (too many surgeons operating few patients), and that there is a lack of reference centers for the treatment of nephrolithiasis.

Lack of equipment or hospital infrastructure apparently are the main obstacles for the practice of Ureteroscopy in all of Brazilian regions. In relation to URS, that that most urologists perform routinely (95% in all regions), the lack of material/infrastructure is a major hindrance, particularly in North and Northeast regions (40% and 31.5%, respectively), precisely those with the lowest HDI (14) and the least amount of health resources. Regarding F-URS practice, in all regions more than 70% of urologists perform the procedure (the technique is well established in Brazil), but the lack of equipment is still a factor to prevent higher number of surgeries (29.3%-51.2%), probably due to the high costs necessary for the equipment acquisition and maintenance, as well as for the short lifespan of flexible ureteroscope and the need of laser devices to treat stones. Lack of resources was less impactful in Southeast than in other regions (29.3% vs. 42-51.2%), probably due to higher HDI rates, higher number of urologists, more RMU programs and endourology fellowships, so more resources are available to provide the use of edge technologies in health care. Recent actions of BSU, such as the recent incorporation of URS in public health services, may contribute to change this reality in Brazil, as it may lead to the destination of more equipment and hospital infrastructure improvements along the country, reinforcing the role of urologists in national health care politics.

This study also highlights the deficiency that still exists in Brazil regarding that practice of PCNL. In most Brazilian regions, except South, only 48-73% of respondents claimed to perform PCNL, being lack of practical experience the main reason (32-34%). These data are in accordance with another Brazilian study that also concluded that the lack of training was the main reason for the low use of PLN (17). In that study, most urologists that performed the technique were young, with adequate training during their medical residency, reinforcing the importance of MRU programs to prepare urologists to perform PCLN. As in ureteroscopy, lack of equipment/hospital infrastructure were observed in the regions with lower HDI (40% North and 32% Northeast), probably due to lower investments in health and education. On the other hand, in South, PCNL is performed by 82% of respondents and only a small proportion of those (13.2%) claimed lack of practical experience with the technique, probably due to a higher number of MRU and urological services that

teach and perform PCNL. These results emphasize the need to encourage PCNL teaching programs by hands-on courses or by increasing of the number of procedures during residency. Creating of more referral centers and endourology fellowship programs, particularly in regions other than the South and Southeast, may improve this scenario, since with more procedures the rate of complications and clinical results greatly improves (18, 19).

Finally, this study has shown that most Brazilian urologists are interested in participating in endourology courses (>70% in all regions), and, except in South and Southeast, most urologists would travel more than 200 km to attend these courses, probably due to the fact that most are located in those more developed regions, with better infrastructure and higher concentration of urologists.

However, the results of our study must be interpreted carefully, and some limitations must be taken into account: it was based on a volunteer electronic question form, only 25% of BSU members answered the questionnaire, there may have been a higher participation of younger urologists, those from academic centers or those with more expertise in endourology, that could have overestimated the percentage of urologists familiar with those techniques to surgically treat kidney stones, with a higher number of procedures. On the other hand, due to the same reasons, since many respondents indicated lack of practical experience in PCNL, this information is even more relevant, since there could be many more general urologists that need training. Also, it was not possible to determine if the respondents practiced mainly in private or public health services, what could have influenced surgical daily practice. Usually, public services suffer from lack of resources and surgical material, while private services usually perform more procedures with lower morbidity potential and higher remuneration, such as flexible ureteroscopy instead of PCNL. Other aspects were not addressed, such as age influence and remuneration of the procedures, as well as availability of extracorporeal lithotripsy as an alternative method to treat kidney stones. All these aspects should be evaluated in future studies but, nevertheless, the results of this study reflect the status of a great proportion of Brazilian urologists equally distributed in the country, providing important information about the current scenario of endourology in Brazil. More studies sponsored by BSU should be encouraged to deepen the understanding of endourology practices in our country, providing data to propose new courses and actions directed to improve the main deficits of this area.

CONCLUSIONS

This study was able to present important information regarding current scenario of endourology in Brazil. Ureteroscopy, flexible or rigid, are well stablished in the country, and more resources are necessary to improve their practice, mainly in underdeveloped regions. Regarding PNL, a significant part of Brazilian urologists still have no practical experience with the method, and more teaching efforts should be made.

ABBREVIATIONS

PCNL = percutaneous nephrolithotomy;
URS = rigid ureteroscopy;
F-URS = flexible ureteroscopy;
MRU = Medical Residency in Urology
BSU = Brazilian Urological Society

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Turney BW, Reynard JM, Noble JG, Keoghane SR. Trends in urological stone disease. BJU Int. 2012;109:1082-7.
2. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Soda and other beverages and the risk of kidney stones. Clin J Am Soc Nephrol. 2013;8:1389-95.
3. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62:160-5.
4. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int. 2003;63:1817-23.

5. Saigal CS, Joyce G, Timilsina AR; Urologic Diseases in America Project. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? Kidney Int. 2005;68:1808-14.
6. Curhan GC. Epidemiology of stone disease. Urol Clin North Am. 2007;34:287-93.
7. [No Authors]. Brasil. Ministério da Saúde. Datasus. Morbidade hospitalar do SUS por local de internação - Brasil. 2017. Available at. <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/niuf.def> [accessed on 2018 October 23]
8. Oberlin DT, Flum AS, Bachrach L, Matulewicz RS, Flury SC. Contemporary surgical trends in the management of upper tract calculi. J Urol. 2015;193:880-4.
9. Ghani KR, Sammon JD, Karakiewicz PI, Sun M, Bhojani N, Sukumar S, et al. Trends in surgery for upper urinary tract calculi in the USA using the Nationwide Inpatient Sample: 1999-2009. BJU Int. 2013;112:224-30.
10. Ather MH, Paryani J, Memon A, Sulaiman MN. A 10-year experience of managing ureteric calculi: changing trends towards endourological intervention--is there a role for open surgery? BJU Int. 2001;88:173-7.
11. Kerbl K, Rehman J, Landman J, Lee D, Sundaram C, Clayman RV. Current management of urolithiasis: progress or regress? J Endourol. 2002;16:281-8.
12. Marchini GS, Mello MF, Levy R, Vicentini FC, Torricelli FC, Eluf-Neto J, et al. Contemporary Trends of Inpatient Surgical Management of Stone Disease: National Analysis in an Economic Growth Scenario. J Endourol. 2015;29:956-62.
13. Scheffer, M. et al. Demografia Médica no Brasil 2018. São Paulo, SP: FMUSP, CFM, Cremesp, 2018. 286 p. ISBN: 978-85-87077-55-4.
14. Desenvolvimento humano nas macrorregiões brasileiras: 2016. Brasília: PNUD: IPEA: FJP, 2016. 55 p.: il., gráfs., mapas color.
15. Lee MC, Bariol SV. Evolution of stone management in Australia. BJU Int. 2011;108(Suppl 2):29-33.
16. Ordon M, Urbach D, Mamdani M, Saskin R, D'A Honey RJ, Pace KT. The surgical management of kidney stone disease: a population based time series analysis. J Urol. 2014;192:1450-6.
17. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69:475-82.
18. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART I. J Urol. 2016;196:1153-60.
19. Batagello CA, Vicentini FC, Marchini GS, Torricelli FCM, Srougi M, Nahas WC, et al. Current trends of percutaneous nephrolithotomy in a developing country. Int Braz J Urol. 2018;44:304-313.
20. Opondo D, Tefekli A, Esen T, Labate G, Sangam K, De Lisa A, et al. Impact of case volumes on the outcomes of percutaneous nephrolithotomy. Eur Urol. 2012;62:1181-7.
21. Kadlec AO, Ellimoottil C, Guo R, Trinh QD, Sun M, Turk TM. Contemporary volume-outcome relationships for percutaneous nephrolithotomy: results from the Nationwide Inpatient Sample. J Endourol. 2013;27:1107-13.

Correspondence address:
Rafael Haddad Astolfi, MD
Disciplina de Urologia,
Universidade Federal de São Paulo – UNIFESP,
São Paulo, SP, Brasil
Telephone: + 55 (11) 99797-0045
E-mail: rafael.astolf95@gmail.com

ORIGINAL ARTICLE

Vol. 46 (3): 409-416, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0367

Lessons learned after 20 years' experience with penile fracture

Rodrigo Barros [1], Daniel Hampl [1], Andre Guilherme Cavalcanti [2], Luciano A. Favorito [3], Leandro Koifman [1]

[1] Serviço de Urologia, Hospital Municipal de Souza Aguiar, Rio de Janeiro, RJ, Brasil; [2] Disciplina de Urologia, Universidade Federal do Estado do Rio de Janeiro - Unirio, Rio de Janeiro, RJ, Brasil; [3] Unidade de Pesquisa Urogenital, Universidade Estadual do Rio de Janeiro – UERJ, Rio de Janeiro, RJ, Brasil

ABSTRACT

Objective: To report our experience over the past 20 years in the diagnosis and surgical treatment of penile fracture (PF).
Materials and methods: Between January 1997 and January 2017, patients with clinical diagnosis of PF were admitted to our facility and retrospectively assessed. Medical records were reviewed for clinical presentation, etiology and operative findings. Postoperative complications, sexual and urinary function were evaluated.
Results: Sexual trauma was the main etiological factor, responsible for 255 cases (88.5%): 110 (43.1%) occurred with the "doggy style" position, 103 (40.3%) with "man on top" position, 31 (12.1%) with the "woman on top" position and 11 (4.3%) in other sexual positions. The most common findings in the clinical presentation were hematoma, in all cases and detumescence in 238 (82.6%). Unilateral corpus cavernosum injuries were found in 199 (69%) patients and bilateral in 89 (31%) patients. Urethral injuries were observed in 54 (18.7%) cases. Nine (14.7%) patients developed erectile dysfunction and eight (13.1%) had penile curvature. Only two (3.7%) patients had complications after urethral reconstruction.
Conclusions: PF has typical clinical presentation and no need for additional tests in most cases. Hematoma and immediate penile detumescence are the most common clinical findings. Sexual activity was the most common cause. The 'doggy style' and 'man-on-top' was the most common positions and generally associated with more severe lesions. Concomitant urethral injury should be considered in cases of high-energy trauma. Surgical reconstruction produces satisfactory results, however, it can lead to complications, such as erectile dysfunction and penile curvature.

ARTICLE INFO

Luciano Alves favorito
http://orcid.org/0000-0003-1562-6068

Keywords:
Penile Erection; Penis; Learning

Int Braz J Urol. 2020; 46: 409-16

Submitted for publication:
June 08, 2019

Accepted after revision:
August 30, 2019

Published as Ahead of Print:
October 30, 2019

INTRODUCTION

Penile fracture (PF) is a relatively uncommon form of urologic trauma. Vaginal intercourse is the most common cause of PF (1), but non-coital etiology (masturbation or penile manipulation) is also reported, especially in some Middle Eastern countries (2). Generally, patients report hearing a cracking noise during sexual activity, followed by immediate pain and penile detumescence, in addition to the emergence of large edema and hematoma, leading to an 'eggplant deformity' (3). Diagnosis is typically clinical. However, in doubtful cases, additional examinations such as ultraso-

nography (USG) and magnetic resonance imaging (MRI) can be used for diagnostic confirmation (4). The treatment is usually surgical, where closure of the tunica albuginea is used to prevent sequelae such as erectile dysfunction (ED), curvature and painful erections (5).

The aim of this study is to report our experience over the past 20 years in the diagnosis and surgical treatment of PF along with the long-term outcomes.

MATERIAL AND METHODS

Between January 1997 and January 2017, 285 patients with clinical diagnosis of PF were admitted to our facility and retrospectively assessed. Our institution is the biggest urologic emergency unit in Rio de Janeiro, a metropolitan area in Brazil with more than 6 million inhabitants.

The medical records were systematically reviewed for epidemiological data, history and clinical presentation, etiology, and operative findings. Primary diagnosis assessment was performed through clinical history and physical examination. Complementary imaging methods such as USG and MRI of the penis were performed only in doubtful cases. Retrograde urethrography (RGU) was performed in selected cases when urethral injury was suspected.

All patients underwent surgical treatment immediately after diagnosis. The technique standardized in our institution, as previously described (6), is a circular sub-coronal incision and degloving of the penis, followed by debridement and synthesis of the injury, using simple interrupted sutures of 3-0 polyglactin. The urethral injuries are repaired using simple interrupted sutures of 5-0 polyglactin placed under a Foley catheter. Postectomy is performed routinely in all uncircumcised patients.

From the third month after surgery, all patients with urethral lesion answered the IPSS questionnaire (International Prostate Symptom Score) and underwent uroflowmetry. Patients having altered IPSS or uroflowmetry underwent RGU to exclude or confirm urethral stenosis. Six months after surgery, patients who reported having acquired curvature underwent a drug-induced erection test using alprostadil 10mcg, to evaluate the exact type and degree of curvature. The evaluation of the postoperative erectile function was performed by completing the International Index of Erectile Function (IIEF-5). Penile color duplex doppler ultrasound (CDDU) was performed for those who had persistent ED to obtain a precise etiological diagnosis.

Regarding statistical analyses, correlations between target events were assessed using Pearson's correlation coefficient. The chi-squared or Fisher's exact test, when appropriate, was employed for contingency table analyses. P-value <0.05 was considered significant.

The experimental protocol was approved by our institution's ethics and human research committee. The patients who refused to sign informed consent form or those who underwent incomplete follow-up were excluded.

RESULTS

From a total of 285 patients evaluated in this study, we identified 288 cases of PF (3 patients presented an additional PF after the primary episode). The patient's age ranged from 18 to 69 years (mean 38.2 years). Time elapsed between trauma and hospital admission ranged from 2 to 504 hours (mean 18.5 hours).

Investigation of the mechanism of injury revealed sexual trauma as the main etiological factor, responsible for 255 cases (88.5%). Masturbation was reported by nine patients (3.1%). For non-sexual injury mechanisms, we found penile manipulation in 18 cases (6.2%) and rolling in bed in one case (0.3%). Five patients (1.7%) refused to provide data on the injury mechanism.

Of the 255 cases in which the etiology was sexual intercourse, 110 (43.1%) cases occurred with the "doggy style" position, 103 (40.3%) with "man on top" position, 31 (12.1%) with the "woman on top" position and 11 (4.3%) in other sexual positions.

The most common findings in the clinical presentation were hematoma in all cases (100%), detumescence in 238 (82.6%), a snapping sound in 220 (76.3%), pain in 191 (66.3%), urethral bleeding in 37 (12.8%), and acute urinary retention

in one (0.3%). All patients with urethral bleeding or acute urinary retention had experienced some degree of urethral injury.

Imaging tests were performed on 46 (16.1%) patients, of whom 19 (6.6%) underwent USG and two (0.7%) underwent MRI of the penis. The remaining 25 (8.7%) patients with suspected urethral injury underwent retrograde urethrography and diagnostic confirmation was achieved in all cases.

Unilateral injuries of the corpus cavernosum were found in 199 patients (69%) and bilateral injuries were identified in 89 (31%) patients. Urethral injuries were observed in 54 cases (18.7%), including 39 (13.5%) partial injuries and 15 (5.2%) total injuries. The complete rupture of the urethra was associated with bilateral injury in the corpus cavernosum in 100% of cases (Figure-1). Of three patients with refracture, all presented the second episode with injury at the same point as the primary repair and contralateral involvement was observed in only one case. Demographic data and intra-operative findings are summarized in Table-1.

Of the 285 patients, 61 participated in follow-up of at least six months (mean 11.6). Forty-four (72.1%) patients developed penile nodule, 8 (13.1%) patients had penile curvature and 9 (14.7%) patients developed ED, of which 1 needed to perform penile color duplex doppler ultrasound with pharmacological induced erection test with alprostadil intracavernous injection to exclude vascular disease (Figure-2). Our data did not identify a statistical difference between the time of PF repair and ED or penile curvature rates. Of the 54 cases with associated urethral lesion, only two (3.7%) patients had complications (urethro-cutaneous fistula and subcutaneous abscess adjacent to the anastomosis area). Two (3.2%) patients presented necrosis of the operative wound (Figure-3). Postoperative complications are demonstrated in Table-2.

Figure 1 - Complete rupture of the urethra associated with bilateral injury in the corpus cavernosum.

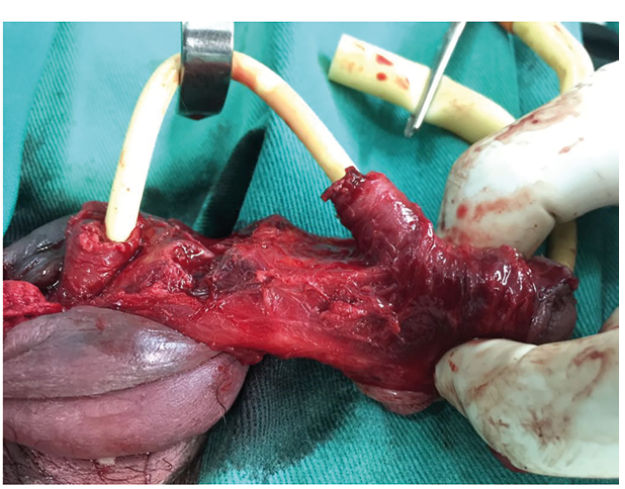


Table 1- Demographic data and intra-operative findings.

Cases (N)	288
Average age (years)	38.2 (18-69)
Etiology	
Sexual intercourse	255 (88.5%)
Masturbation	09 (3.1%)
Penile manipulation	18 (6.2%)
Rolling in bed	01 (0.3%)
Patients refused to provide data	
Signs and' symptoms	05 (1.7%)
Hematoma	288 (100%)
Detumescence	238 (82.6%)
Snapping sound	220 (76.3%)
Pain	191 (66.3%)
Urethral bleeding	37 (12.8%)
Acute urinary retention	01 (0.88%)
Rupture of the tunica albuginea	
Unilateral	199 (69%)
Bilateral	89 (31%)
Urethral injury	
Partial	39 (13.5%)
Complete	15 (5.2%)

DISCUSSION

While PF is an uncommon urological injury, its incidence is probably underestimated, since patients might not seek medical treatment in emergency rooms due to embarrassment. This fact, combined with the poor public health system in Brazil, may explain the long time lapse observed in this study between the occurrence of the trauma and

Figure 2 - Penile color duplex Doppler ultrasound after pharmacological induced erection test through Alprostadil intracavernous injection excluding vascular disease in a patient with erectile dysfunction after a penile fracture.

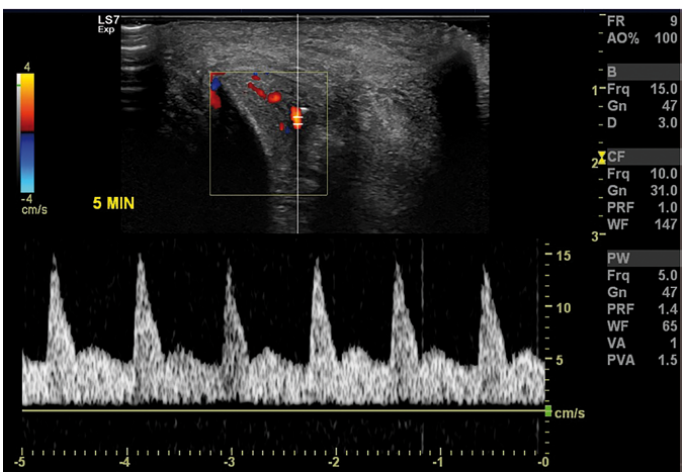


Figure 3 - A-Necrosis of the surgical wound after circumcision B - Satisfactory evolution after conservative treatment with local dressings and with and secondary healing.

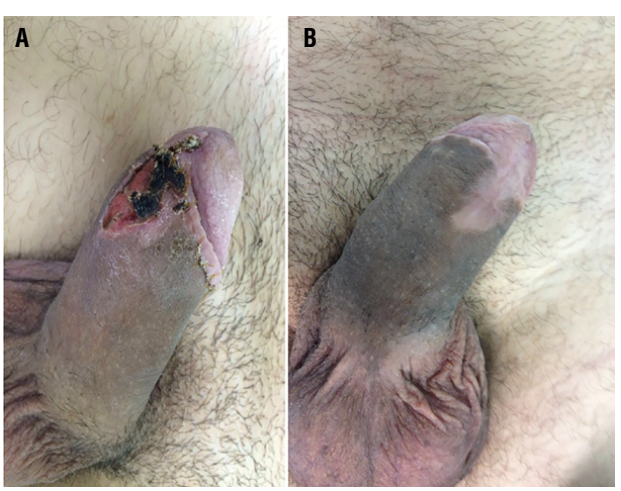


Table 2 - Postoperative complications after penile fracture surgical treatment.

Complications	Cases (%)
Penile curvature	08 (13.1)
Erectile dysfunction	09 (14.7)
Penile nodule	44 (72.1)
Urethro-cutaneous fistula	01 (1.6)
Subcutaneous abscess	01 (1.6)
Necrosis of the operative wound	02 (3.2)

hospital admission, which ranged from 2 to 504 hours (mean 18.5 hours). Even with treatment delay of 21 days, we did not identify a statistical difference between the time of PF repair and complications such as ED or penile curvature rates.

There are several causes of PF described in the literature in different regions of the world. The most common etiology in Western countries is sexual intercourse (4, 7). In Eastern countries, there is a higher incidence of cases associated with penile manipulation due to the practice of "thagaandan" in which the patients bends the distal portion of the penile shaft while holding the proximal part in place to achieve forced detumescence (2). Other practices, such as masturbation, falling on an erect penis, and rolling in bed have also been reported as causes in previous studies (8). El Atat et al. (9) described their experience with 300 cases of penile fractures and the etiology was masturbation in 180 cases (60%), rolling over in bed in 63 cases (21%), and sexual intercourse in 57 cases (19%). In our study, we observed that sexual activity was the most common mechanism of trauma, represented mainly by sexual intercourse (88.5%). As noted in a previous article by our group, the 'doggy style' and

'man-on-top' positions showed more associations with severe lesions such as bilateral fractures of the corpus cavernosum and urethral lesions (10).

PF is more common in younger individuals, with mean ages mostly in the fourth decade (7, 11). In our series, the patient's age ranged from 18 to 69 years (mean 38.2 years).

The recurrence of PF is even rarer, with few cases described in the international literature (12). We found only three (1%) patients with refracture. All presented the second episode with injury at the same point as the primary repair, but contralateral involvement was observed only in one case.

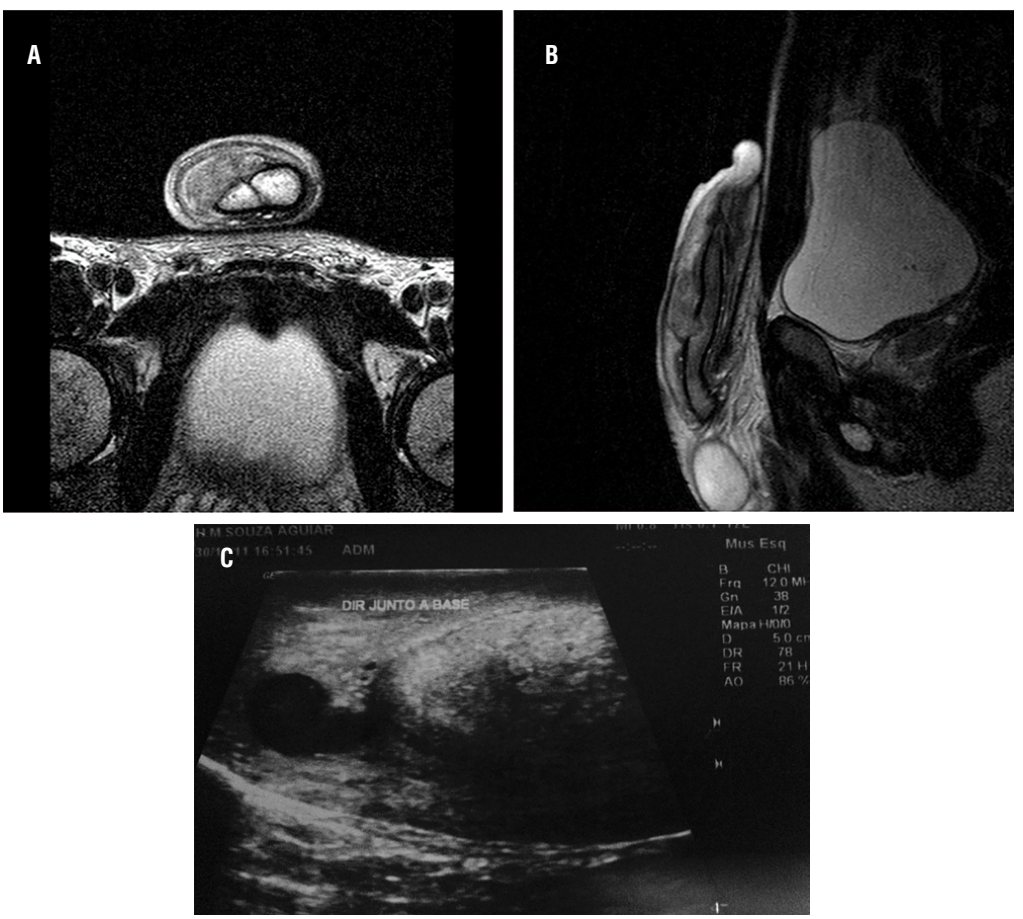
For most authors, the diagnosis of PF is eminently clinical, with no need for additional tests since there is a typical clinical presentation. The typical triad of hematoma, detumescence, and snapping sound is a key diagnostic finding in the initial evaluation of these patients. According to Zargooshi (2), considering the excellent accuracy of clinical diagnosis, there is no need for any ancillary diagnostic test. Of 362 operated patients, 352 were intraoperatively proven to have PF and 10 had penile venous injury only. Diagnosis of PF in these 10 cases was made by our junior residents, who themselves operated on the patients. In a study conducted by Koifman et al. (4), the authors introduced the concept of penile trauma with low suspicion of PF in the assessment of doubtful cases. This new concept describes patients with a blunt trauma of the erect penis and no pain or immediate penile detumescence after the traumatic event, the presence of mild to moderate hematoma; and physical examination results, including palpation of the uninjured corpora cavernosa. A recent metanalysis reveals that 31 authors used no imaging, 22 authors used various image modalities to confirm the diagnosis: USG, cavernography, RGU and MRI (13). In our study, all patients showed penile hematoma upon admission, associated with detumescence in 82.6% of cases and a snapping sound in 76.3%. Only 6.6% doubtful cases underwent USG and 0.7% underwent MRI of the penis (Figure-4). RGU may show false-negative results in up to 28.5% of cases (14). Although RGU was performed in 25 of our cases, we believe that complementary examination is not necessary in cases of suspected urethral lesion in which penile degloving technique provides excellent exposure of the urethra and corpus cavernosum in all their extension. Urethral lesions are easily detected in the intraoperative period. Proof of this is that in the last 13 patients, RGU was performed in only one case.

Although according to most series the diagnosis of PF is made only by clinical findings, USG can be used to confirm the diagnosis and localize the site of the albuginea rupture and exclude the presence of urethral lesion.

This allows the access to the exact point of injury through a small skin incision avoiding the complications of degloving and postectomy (15) Mazaris (16), presented their experience with immediate surgical repair of eight patients with PF, using a midline ventral incision on the penile raphe. In six patients the diagnosis was confirmed by USG. According to the authors, this approach achieves good early and late results, has the advantage of direct access to both corpora cavernosa and the anterior urethra, with a minimal skin incision. More recently, Mao (17), described a study with 46 cases of PF treated using coronal proximal circular incision in 16 and local longitudinal incision in the other 30, according to the rupture location on USG. Fourteen of the 16 cases of circular degloving incision presented short-term postoperative foreskin edema but no postoperative complications were observed in any of the cases of local incision. The authors concluded that local longitudinal incision is sufficient to repair the tunica albuginea, without affecting the blood supply or lymph reflux, with low rate of complications. However, they defend the degloving when bilateral lesions of the corpora cavernosa and urethral injury are present. Circular sub-coronal incision and degloving of the penis with postectomy in uncircumcised patients was the technique standardized in our study. We found postoperative skin necrosis in two of 288 cases, accounting for only 0.6% of our total sample.

The presence of urethral injury associated with PF was reported as 3-38% (18). It is usually associated with high-energy trauma resulting in bilateral corpora cavernosa involvement. El-Assmy et al. (19) reported 14 cases of urethral injury

Figure 4 - Patient with doubtful clinical picture of PF submitted to penile MRI demonstrating right corpus cavernosum base rupture with moderate hematoma in axial and sagittal images (A+B). Ultrasound demonstrating right corpus cavernosum base rupture with mild hematoma in another patient with doubtful clinical picture of PF (C).



and all lesions were located at the same level as the corpus cavernosum, which were partial in 11 cases and complete in three. All patients had normal urinary flow except one, who developed relative urethral narrowing that required regular dilatation for one month. AAmong 312 cases of PF, Derouiche et al. (20) performed a retrospective study of a series of 10 cases of urethral lesion where no urethral stricture was noted after reconstruction.

In our study, urethral injuries were observed in 18.7% of cases, including 39 (13.5%) partial injuries and 15 (5.2%) total injuries. The complete rupture of the urethra was associated with bilateral injury in the corpus cavernosum in all cases. Only two (3.7%) patients had complications after urethral reconstruction (urethro-cutaneous fistula and subcutaneous abscess adjacent to the anastomosis area).

The surgical treatment of PF can lead to several long-term sexual complications. Zargooshi (2) evaluated 352 PF operated patients, and eight had sexual complaints at follow-up including premature ejaculation, ED, hypodesire disorder, anxiety, depression and marital conflict. El Atat et al. (9) described their experience with 300 cases of PF and observed complications in 40 patients (13.3%), of whom 14 (23.3%) developed penile curvature, 10 had penile nodules (3.34) and two suffered from erectile dysfunction (0.6%). In our study, of 61 patients that participated in follow-up of at least six months, nine (14.7%) developed ED and eight (13.1%) had penile curvature.

Some limitations of this study should be mentioned: The data are limited by the retrospective nature of the study but to our knowledge, this is the fourth largest case series published in the literature.

CONCLUSIONS

PF has typical clinical presentation and does not need any additional tests in most cases. Hematoma and immediate penile detumescence after the traumatic event are the most common findings. Recurrent FP is extremely rare. Nevertheless, ipsilateral and even contralateral rupture of the prior PF may be present. Sexual activity is the most common cause. The 'doggy style' and 'man-on-top' positions are the most common and are generally associated with more severe lesions. Concomitant urethral injury should always be considered in cases of high-energy trauma, such as bilateral injuries in the corpora cavernosa and urethral bleeding or acute urinary retention. There is no ideal time of repair and a delay of a few days may be acceptable without interfering with the results. Surgical reconstruction produces satisfactory results. However, it can lead to complications, especially ED and penile curvature.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Eke N. Fracture of the penis. Br J Surg. 2002;89:555-65.
2. Zargooshi J. Sexual function and tunica albuginea wound healing following penile fracture: An 18-year follow-up study of 352 patients from Kermanshah, Iran. J Sex Med. 2009;6:1141-50.
3. Ateyah A, Mostafa T, Nasser TA, Shaeer O, Hadi AA, Al-Gabbar MA. Penile fracture: surgical repair and late effects on erectile function. J Sex Med. 2008;5:1496-502.
4. Koifman L, Barros R, Júnior RA, Cavalcanti AG, Favorito LA. Penile fracture: diagnosis, treatment and outcomes of 150 patients. Urology. 2010;76:1488-92.
5. Ibrahiem el-HI, el-Tholoth HS, Mohsen T, Hekal IA, el-Assmy A. Penile fracture: long-term outcome of immediate surgical intervention. Urology. 2010;75:108-11.
6. Koifman L, Cavalcanti AG, Manes CH, Filho DR, Favorito LA. Penile fracture - experience in 56 cases. Int Braz J Urol. 2003;29:35-9.
7. Hatzichristodoulou G, Dorstewitz A, Gschwend JE, Herkommer K, Zantl N. Surgical management of penile fracture and long-term outcome on erectile function and voiding. J Sex Med. 2013;10:1424-30.
8. Taha SA, Sharayah A, Kamal BA, Salem AA, Khwaja S. Fracture of the penis: surgical management. Int Surg. 1988;73:63-4.
9. El Atat R, Sfaxi M, Benslama MR, Amine D, Ayed M, Mouelli SB, et al. Fracture of the penis: management and long-term results of surgical treatment. Experience in 300 cases. J Trauma. 2008;64:121-5.
10. Barros R, Schulze L, Ornellas AA, Koifman L, Favorito LA. Relationship between sexual position and severity of penile fracture. Int J Impot Res. 2017;29:207-9.
11. Hinev A. Fracture of the penis: treatment and complications. Acta Med Okayama. 2000;54:211-6.
12. Ridyard DG, Phillips EA, Munarriz R. Recurrent Penile Fracture: A Case Report and Review of Literature. J Integr Nephrol Androl 2015; 2:132-4.
13. Amer T, Wilson R, Chlosta P, AlBuheissi S, Qazi H, Fraser M, et al. Penile Fracture: A Meta-Analysis. Urol Int. 2016;96:315-29.
14. Mydlo JH, Hayyeri M, Macchia RJ. Urethrography and cavernosography imaging in a small series of penile fractures: a comparison with surgical findings. Urology. 1998;51:616-9.
15. Falcone M, Garaffa G, Castiglione F, Ralph DJ.Current Management of Penile Fracture: An Up-to-Date Systematic Review. Sex Med Rev. 2018;6:253-60.
16. Mazaris EM, Livadas K, Chalikopoulos D, Bisas A, Deliveliotis C, Skolarikos A. Penile fractures: immediate surgical approach with a midline ventral incision. BJU Int. 2009 Aug;104(4):520-3.
17. Mao YS, Hua B, Pan WX, Li WF, Gu YF, Yao HJ, Cai ZK, Wang Z, Lu C. Surgical repair of the tunica albuginea for penis fracture: Selection of incision. Zhonghua Nan Ke Xue. 2018 Apr;24(4):331-334.
18. Muentener M, Suter S, Hauri D, Sulser T. Long-term experience with surgical and conservative treatment of penile fracture. J Urol. 2004;172:576-9.

19. El-Assmy A, El-Tholoth HS, Mohsen T, Ibrahiem el HI. Long-term outcome of surgical treatment of penile fracture complicated by urethral rupture. J Sex Med. 2010;7:3784-8.
20. Derouiche A, Belhaj K, Hentati H, Hafsia G, Slama MR, Chebil M. Management of penile fractures complicated by urethral rupture. Int J Impot Res. 2008;20:111-4.

Correspondence address:
Leandro Koifman, MD
Serviço de Urologia,
Hospital Municipal de Souza Aguiar,
Praca da República, 111
Rio de Janeiro, RJ, 20211-350, Brasil
E-mail: lekoifman@gmail.com

EDITORIAL COMMENT

Vol. 46 (3): 417-418, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0367.1

Editorial Comment: Lessons learned after 20 years' experience with penile fracture

Aderivaldo Cabral Dias Filho [1, 2], Homero Ribeiro [1]

[1] *Unidade de Urologia do Hospital de Base do Distrito Federal, DF, Brasil; 2 Disciplina de Urologia, Departamento de Cirurgia, Faculdade de Ciências Médicas, Universidade Estadual de Campinas - UNICAMP, Campinas, SP, Brasil*

COMMENT

The article describes the authors' 20-year experience with penile fracture, gained from their work at largest emergency department of the city of Rio de Janeiro (1). This study follows previous publications on the subject of penile fracture by the same group of authors (2-4), and provides the practising urologist with valuable information about the diagnosis and treatment of the disease.

Although there is justifiable debate about whether one should surgically approach penile fractures through a subcoronal (the authors' - and ours' - choice), penoescrotal or perineal incision, the attending urologist must first determine whether the patient has, in fact, a penile fracture, or a vascular injury mimicking a penile fracture, i.e. a false penile fracture (5-7). The authors' no-nonsense approach to this diagnostic problem was to consider patients that did not describe immediate detumescence after injury, presenting small-to-moderate penile hematoma (or none at all) and without abnormalities in the palpation of the corpora cavernosa as having a lower likelihood of penile fracture - and offer to these patients supplemental imaging studies or conservative treatment with close follow-up. The reader must be cautioned, however, that such line of action is grounded by the authors' large experience, and that the default approach in clinically diagnosed penile fracture patients is surgical exploration.

Another facet of the authors' large experience with the disease can be observed in their approach to synchronous urethral injuries, diagnosed in 54 of their patients (18.7%). Preoperative retrograde urethrography (RUG) was performed in a little less than half of those (25/54, 47%), and their logic in restricting the indication of RUG is simple to follow: Urethral injuries are not rare in penile fracture; RUG has been associated with high false-negative rates (reference 14 in the article); penile degloving provides excellent exposure to the penile urethra; urethral repair can be easily performed concomitant with tunical repair; ergo, one can forgo RUG in these cases. Yet, one should not promptly waive RUG if the surgical plan involves an incision directly to the site of injury, even more so if there is any sign of urethral injury, e.g. urethral bleeding, urinary retention.

Our last comment addresses the fact that the study included 285 patients and 288 penile fractures, as 3 patients had a recurrent fracture - at the same site as the first one. This finding calls to attention that changes in the biomechanical properties of the tunica albuginea at the site of injury predosposes the organ to repeat fracture. The last consideration regards the patient's behavior during the sexual act. Since the persistence of the sexual behavior that caused the fracture may lead to a recurrent fracture, one can conjecture that the sparseness of recurrent fractures may stem from modifications in sexual behavior - decreases in the frequency of intercourse, avoidance of certain positions, for ins-

tance - likely associated with the already documented negative long-term psychological impact of the disease (8). Such modifications in sexual behavior, while detrimental to the patient's and partner's quality-of-life, may subliminally protect the patient against another frature. Perhaps one lesson to be learned from this is that penile fracture patients may benefit from more detailed information about the mechanism of fracture, as well as from sexual counseling.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Barros R, Hampl D, Cavalcanti AG, Favorito LA, Koifman L. Lessons learned after 20 years' experience with penile fracture. Int Braz J Urol. 2020;46: 409-16.
2. Koifman L, Cavalcanti AG, Manes CH, Filho DR, Favorito LA. Penile fracture - experience in 56 cases. Int Braz J Urol. 2003;29:35-9.
3. Koifman L, Barros R, Júnior RA, Cavalcanti AG, Favorito LA. Penile fracture: diagnosis, treatment and outcomes of 150 patients. Urology. 2010;76:1488-92.
4. Barros R, Silva M, Antonucci V, Schulze L, Koifman L, Favorito LA. Primary urethral reconstruction results in penile fracture. Ann R Coll Surg Engl. 2018;100:21-5.
5. El-Assmy A, El-Tholoth HS, Abou-El-Ghar ME, Mohsen T, Ibrahiem el HI. False penile fracture: value of different diagnostic approaches and long-term outcome of conservative and surgical management. Urology. 2010;75:1353-6.
6. Feki W, Derouiche A, Belhaj K, Ouni A, Ben Mouelhi S, Ben Slama MR, et al. False penile fracture: report of 16 cases. Int J Impot Res. 2007;19:471-3.
7. Dias-Filho AC, Fregonesi A, Martinez CAT, Pimentel ES, Riccetto CLZ. Can the snapping sound discriminate true from false penile fractures? Bayesian analysis of a case series of consecutively treated penile fracture patients. Int J Impot Res. 2019 Sep 24. [Epub ahead of print].
8. Bolat MS, Özen M, Önem K, Açıkgöz A, Asci R. Effects of penile fracture and its surgical treatment on psychosocial and sexual function. Int J Impot Res. 2017;29:244-9.

ARTICLE INFO

Aderivaldo Cabral Dias Filho
https://orcid.org/0000-0002-2648-8679

Int Braz J Urol. 2020; 46: 417-8

Submitted for publication:
January 15, 2020

Accepted after revision:
February 10, 2020

Aderivaldo Cabral Dias Filho, MD

Disciplina de Urologia, Departamento de Cirurgia
Faculdade de Ciências Médicas, Universidade Estadual de Campinas – UNICAMP
Rua Tessália Vieira de Camargo, 126. Cidade Universitária Zeferino Vaz. CEP 13083-887 – Campinas, SP, Brasil
E-mail: aderivaldo.uro@gmail.com

ORIGINAL ARTICLE

Vol. 46 (3): 419-424, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0402

Detrusor underactivity versus bladder outlet obstruction clinical and urodynamic factors

Jefferson Kalil [1], Carlos Arturo Levi D´Ancona [1]

[1] *Escola de Ciências Médicas, Universidade Estadual de Campinas – Unicamp, Campinas, SP, Brasil*

ABSTRACT

Objectives: To evaluate the lower urinary tract symptoms, classified by the International Prostate Symptom Score (IPSS), urodynamic results (Watts Factor (WF), Bladder Contractility Index (BCI), and post void residual (PVR), in order to differentiate Detrusor Underactivity (DU) from Bladder Outlet Obstruction (BOO).
Methods: Retrospective observational study performed from 2011 to 2018 at the Hospital das Clínicas of Unicamp. Two phases were done: first, to estimate sample size, and second, to evaluate the predicted parameters. Male patients with range age from 40 to 80 years were included. Patients were divided into two groups: Group 1, without BOO and with DU; Group 2, with BOO. Variables analyzed: age, comorbidities, symptoms, urodynamic data (BCI and WF) and PVR.
Results: Twenty-two patients were included in each group, with medians of 68 (Group 1) and 67.5 years old (Group 2) (p = 0.8416). There was no difference for comorbidities. In relation to IPSS, medians were: 16.5 and 20.5, respectively (p = 0.858). As for symptoms, there was predominance of combination of storage and voiding symptoms in the two groups (p = 0.1810). Regarding PVR, 15 patients in Group 1 and 16 in Group 2 presented PVR> 30mL (p = 0.7411). BCI presented median values of 75 and 755.50 for Group 1 and Group 2, respectively (p <0.0001), while WF had medians of 22.42 and 73.85 (p <0.0001).
Conclusion: Isolated symptoms, classified by IPSS and PVR, could not differentiate patients with DU from those with BOO, but it was possible using urodynamic data.

ARTICLE INFO

Jefferson Kalil
http://orcid.org/0000-0001-6624-8074

Keywords:
Urodynamics; Urinary Bladder, Underactive; Lower Urinary Tract Symptoms

Int Braz J Urol. 2020; 46: 419-24

Submitted for publication:
June 18, 2019

Accepted after revision:
January 18, 2020

Published as Ahead of Print:
February 10, 2020

INTRODUCTION

Detrusor underactivity (DU) according to the International Continence Society (ICS) includes low detrusor pressure or short detrusor contraction time, usually in combination with a low urine flow rate resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span (1). This definition, although adequate, does not show the parameters that define this diagnosis: method used to measure strength, value of normality and appropriate urination time.

In general, the most prevalent symptoms in men with DU are: reduction and/or interruption of urinary flow, hesitancy, incomplete emptying sensation, palpable bladder, absence and/or reduction of sensitivity, and effort to urinate (2). Recently, si-

milarly to what occurs with the Overactive Bladder, a new clinical syndrome has been suggested, called Underactive Bladder Syndrome, which presents the following symptoms: prolonged urination time with or without feeling of incomplete emptying, usually with hesitancy, reduced sensation of filling, and weak stream (3). Nevertheless, neither the symptoms nor the urodynamic criteria that define DU are well defined so far. This is important, since the prevalence of DU is 9% to 23% in men and 12% to 45% in women (4). Differentiating patients with DU associated with bladder outlet obstruction (BOO) from those who present only bladder outlet obstruction is relevant, since the former group may not benefit from surgical treatment, while the latter will certainly do (5). Moreover, patients with DU and chronic urinary retention may develop overflow incontinence and reduced urination output, which are mild complications, in addition to severe complications, such as urinary lithiasis, recurrent urinary tract infections and renal insufficiency (6).

Regarding the diagnosis, it is necessary to use urodynamics, which is an invasive investigation. Classically, detrusor strength has been evaluated by means of pressure/flow studies. It is noteworthy that current methods used to evaluate the detrusor function are: Schafer nomogram (pressure/flow), Bladder Contractility Index (BCI) and Watts Factor (WF) (7).

Schafer nomogram has been used to differentiate patients with DU from patients with BOO (7, 8). BCI is calculated using a simple formula and can be used as screening method for DU, although it may be a method that is not able to differentiate patients with DU from those with BOO (7, 9). Finally, WF is calculated by a mathematical formula that evaluates the power applied on the bladder per area unit, and calculates detrusor strength during an isovolumetric contraction (10, 11).

Considering the limitations of all mentioned methods, two methods which would have few interfering elements were selected: Bladder Contractility Index (BCI) and Watts Factor (WF) (4, 12).

Despite the fact that some evidence suggests symptoms and post void residual can indicate DU, the information is not well consolidated and the differentiation between DU and BOO remains a problem.

The aim of this study is to evaluate the validity of the lower urinary tract symptoms (LUTS), International Prostate Symptom Score (IPSS), BCI, WF and post void residual to differentiate DU from BOO.

PATIENTS AND METHODS

Comparative retrospective cross-sectional observational study performed between two groups: Group 1, patients without BOO and with diagnosis of DU, Group 2, patients with BOO. Two phases were performed: the first one, in order to calculate the sample size, and the second, with the final results. Data from the study were obtained from the database of urodynamic exams performed and stored at the Urodynamic Service of HC-UNICAMP (Hospital das Clínicas of the University of Campinas), from patient's medical charts and from HC Computer System. This study was approved by the Ethics Committee in Research, number 1.644.754.

All patients were male and underwent urodynamics between 2011 and 2018. Criteria for inclusion in Group 1 were: absence of obstruction or doubt in ICS Nomogram and presence of weak detrusor in Schafer Nomogram. Inclusion criteria in Group 2 was presence of obstruction in ICS Nomogram. Exclusion criteria were: presence of neurological disease, postoperative of pelvic exenteration, bladder cancer, prostate cancer and patients who underwent prostatic surgery.

In the first phase of the study, 5% significance level (alpha or type I error), and 80% sample power (beta or 20% type II error) were used for sample size calculation. The calculation was made considering the comparison of variables between the two groups. For BCI and WF, 22 and 20 patients were respectively required in each group. Therefore, the sample was enlarged in order to obtain 22 patients in each group.

Besides age and comorbidities, symptoms were analyzed through the International Prostate Symptom Score (IPSS) and classified as storage, voiding, combination of storage and voiding symptoms, and urinary incontinence, urodynamic data: post void residual (PVR) and classification of ICS and Schafer nomograms and calculation of Bladder Contractility Index and Watts Factor.

Categorical variables were described using absolute frequency and percentage, and numerical variables were described as mean, median, standard deviation, minimum and maximum. Mann-Whitney test was used for numerical variables, Chi-square test for PVR and Fisher's exact test for symptoms, considering a 5% significance level.

RESULTS

A total of 44 patients were included in the study, 22 in each group. The average age was 68 years and 67.5 years for Group 1 and Group 2, respectively. (p=0.8416).

Arterial hypertension was present in the same proportion between groups (64%) (p=1.0), while Diabetes Mellitus appeared in 23% of patients in Group 1 and 36% in Group 2 (p=0.51). Dyslipidemia was present in 27% in Group 1 and 18% in Group 2 (p=0.72), and Acute Myocardial Infarction appeared in 23% and 5% patients in Groups 1 and 2, respectively (p=0.18), patients without comorbidities represented 17% in Group 1 and 18% in Group 2 (p=1.0, Fisher's exact test).

For IPSS, the following means were obtained: 16.5 (SD=5.76) for Group 1 and 20.5 (SD=6.94) for Group 2, without significant difference (p=0.858, Mann-Whitney test). For symptoms, the most prevalent category in both groups was the combination of storage and voiding symptoms with 12 patients in Group 1 and 15 patients in Group 2. However, there was not significant difference between groups (p=0.1810, Fisher's exact test).

Post void residual ≥30mL was found in 15 patients in Group 1 and 16 patients in Group 2, without significant difference (p=0.7411, Chi-Square test).

BCI presented median of 75 (SD=120.43) in Group 1, while in Group 2 median was 755.50 (SD=408.12), with significant difference (p <0, 0001, Mann-Whitney Test). For WF, Group 1 showed median of 22.42 (SD=14.88) and Group 2 median of 73.85 (SD=39.86), also with significant difference (p <0.0001, Mann-Whitney test). On the other hand, age and post void residual did not show statistically difference (p=0.8416 and p=0.5327, respectively) (Tables 1 and 2).

Table 1 - Frequency of urodynamic data: measure of detrusor strength by Schafer Nomogram; values of BCI and WF, considering cut-off point values for Detrusor Underactivity.

VARIABLES	GROUP 1 – n (%)	GROUP 2 – n (%)
Schafer		
Very weak	3 (13.64%)	1 (4.55%)
Weak	18 (81.82%)	4 (18.18%)
Normal (-)	1 (4.55%)	-
Normal (+)	-	12 (54.55%)
Strong	-	5 (22.73%)
BCI		
≤ 100	17 (77.27%)	2 (9.09%)
> 100	5 (22.73%)	20 (90.91%)
WF		
≤ 7	7 (31.82%)	2 (9.09%)
> 7	15 (68.18%)	20 (90.91%)

Table 2 - Descriptive and comparative analysis between groups: age, urodynamic data and post void residual; mean, median, standard deviation, minimum, maximum, and confidence intervals were described. There was a significant difference between groups for BCI and WF (p <0.0001; Mann-Whitney test).

VARIABLES	Age (years)		BCI		WF		PVR (mL)	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
N	22	22	22	22	22	22	22	22
Mean	68.23	67.5	125.41	782.82	21.3	73.33	99.36	134.77
Median	68	67.5	75	755.5	22.42	73,85	85	125
Standard Deviation	10.85	9.29	120.43	408.12	14.88	39.86	93.43	146.18
Minimum	50	45	43	68	1.66	2.73	0	0
Maximum	86	83	528	1677	51.37	182	350	620
p	0.8416		<0.0001		<0.0001		0.5327	

BCI = Bladder Contractility Index; **WF** = Watts Factor; **PVR** = Post Void Residual

DISCUSSION

In a recent study comparing patients with DU and BOO, age was not different between groups, as in our study (13). However, it is worth noting that literature shows that DU is more common in the elderly, as demonstrated here, with median age of 68 years (4, 13-15).

Regarding comorbidities, a study comparing these two diseases also showed no difference between groups for hypertension, DM and other diseases, as demonstrated in this study (16). However, it is interesting to note that duration of hypertension (more than 10 years) and DM (more than 6 years) resulted in detrusor contractility changes (13). It is relevant because DM is a disease that leads to nerve damage and deposition of collagen and extracellular matrix in the detrusor, leading to changes on its function (17, 18).

IPSS score, classically described to evaluate the severity of prostate-related symptoms, is presented as a numerical index able to classify symptoms into categories such as mild, moderate or severe. As we have seen, Group 1 did not present statistically difference from Group 2, such as demonstrated by other authors who compared groups of patients with DU and BOO using IPSS score (14). Meanwhile, another study showed a correlation between DU and IPSS, with an association of IPSS between 20-23 and DU (13). Therefore, there is not consensus on validity of IPSS score and its cut-off to DU.

Regarding symptoms, their combination was predominant in both groups in this study, however, an interesting fact is that no patient had only storage symptoms in Group 2, but this information was not significant. Corroborating this information, another study comparing men with DU and BOO showed no difference in symptoms between groups (19). Thus, it seems that the category of symptoms alone cannot differentiate these diagnoses, but it needs to be investigated in further studies.

For BCI, literature places the cut-off value as 100. According to these criteria, BCI <100 corresponds to weak detrusor, between 100-150, normal detrusor, and >150, strong detrusor (12). As observed in Table 2, there is a statistically difference between the groups for BCI, showing that this could be a good parameter, in opposition to what has been presented in other articles that BCI is not able to differentiate patients with DU from those with BOO (8, 20).

The second parameter, Watts Factor, also presented statistical difference between the groups, so it could be a good indicator as well. For WF, li-

terature suggests the value of 7W/m2 as a limit of normality (10). However, although this cut-off has been suggested to the diagnosis of DU, it could be a parameter to differentiate patients with DU from those with BOO (20).

Taking into account the results of our study we suggest the cut-offs of BCI and WF to classify DU and BOO could vary from the classical cut-offs of 7W/m2 to WF and 100 to BCI. However, at present, this cannot be accepted as truth, but should be assessed in future studies.

One study compared Schafer Nomogram, BCI and WF, and showed that only Schafer Nomogram would be able to identify BOO, however, we could observe from the data presented that both BCI and WF were able to differentiate DU from BOO (8).

In another study, there was a correlation among BCI, WF and BOO, inferring that as the degree of bladder outlet obstruction increases, BCI and WF values would increase proportionally. In this line, the authors of that study question the cut-offs used in the diagnosis of DU, suggesting that low values (BCI <100 and WF <7) would be present since there is not BOO and the detrusor muscle is not required to increase its strength in order to compensate resistance. However, when there is DU, there is no increase in detrusor pressure, since there is detrusor failure. Nevertheless, as the study itself presented, there was statistical difference for BCI and WF when compared to Bladder Outlet Obstruction. They questioned both the DU diagnosis criteria and the possible parameters that would compare DU with BOO, but affirmed that these were initial conclusions and needed to be validated (14). One factor to be taken into account is that this compensatory increase could reflect the initial phase of the disease, with the detrusor muscle is still strong, and the second moment, in the evolution of the disease, when it would lose its strength (21). However, in the current studies, there is not reference on the possible DU evolution time and this should be considered in future studies.

One study demonstrated that patients with DU presented high PVR when compared to the control group. In this study, for the diagnosis of DU, the cut-off was 147mL, with sensitivity and specificity of 60.16% and 72.97%, respectively, furthermore, these authors showed that PVR was an independent predictor for DU (13). Although more data suggest that residual volume >40% maximum cystometric capacity would be a strong indicator of DU, it is not a consensus (4). Here, PVR did not show statistical difference between groups, indicating that PVR alone would not be able to differentiate diagnoses, as demonstrated in other studies, which also did not show significant difference between Obstructed and Non-obstructed (14, 19). Thus, although PVR can be calculated using a non-invasive method, such as abdominal ultrasonography, it cannot yet be considered a reliable diagnosis factor, requiring further studies.

The limitations of this study were the small number of patients, the quality of data collected, some missing data, because it is a retrospective study, and the need to classify the symptoms into categories, rather than considering each one separately, because the data collected was registered in categories of symptoms.

CONCLUSIONS

It is possible to conclude that the lower urinary tract symptoms, the International Prostate Symptom Score and post void residual did not show difference between Detrusor Underactivity and Bladder Outlet Obstruction in this study, in contrast, Watts Factor and Bladder Contractility Index were relevant tools in this differentiation.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. D'Ancona C, Haylen B, Oelke M, Abranches-Monteiro L, Arnold E, Goldman H, et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn. 2019;38:433-77.
2. Gammie A, Kaper M, Dorrepaal C, Kos T, Abrams P. Signs and Symptoms of Detrusor Underactivity: An Analysis of Clinical Presentation and Urodynamic Tests From a Large Group of Patients Undergoing Pressure Flow Studies. Eur Urol. 2016;69:361-9.

3. Chapple CR, Osman NI, Birder L, van Koeveringe GA, Oelke M, Nitti VW, et al. The underactive bladder: a new clinical concept? Eur Urol. 2015;68:351-3.
4. Osman NI, Chapple CR, Abrams P, Dmochowski R, Haab F, Nitti V, et al. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. Eur Urol. 2014;65:389-98.
5. Rademakers KL, van Koeveringe GA, Oelke M. Detrusor underactivity in men with lower urinary tract symptoms/ benign prostatic obstruction: characterization and potential impact on indications for surgical treatment of the prostate. Curr Opin Urol. 2016;26:3-10.
6. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21:167-78.
7. Saito M, Yokoi K, Ohmura M, Kondo A. Effects of partial outflow obstruction on bladder contractility and blood flow to the detrusor: comparison between mild and severe obstruction. Urol Int. 1997;59:226-30.
8. Chang YH, Siu JJ, Hsiao PJ, Chang CH, Chou EC. Review of underactive bladder. J Formos Med Assoc. 2018;117:178-184.
9. Schäfer W. Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. World J Urol. 1995;13:47-58.
10. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. BJU Int. 1999;84:14-5.
11. Lecamwasam HS, Yalla SV, Cravalho EG, Sullivan MP. The maximum watts factor as a measure of detrusor contractility independent of outlet resistance. Neurourol Urodyn. 1998;17:621-35.
12. Derek J. Griffiths: Assessment of detrusor contraction strength or contractility. Neurourol Urodyn. 1991; 10: 1-18.
13. Luo F, Sun HH, Su YH, Zhang ZH, Wang YS, Zhao Z, et al. Assessment of noninvasive predictors of bladder detrusor underactivity in BPH/LUTs patients. Int Urol Nephrol. 2017;49:787-92.
14. Oelke M, Rademakers KL, van Koeveringe GA. Detrusor contraction power parameters (BCI and W max) rise with increasing bladder outlet obstruction grade in men with lower urinary tract symptoms: results from a urodynamic database analysis. World J Urol. 2014;32:1177-83.
15. Madersbacher S, Pycha A, Schatzl G, Mian C, Klingler CH, Marberger M. The aging lower urinary tract: a comparative urodynamic study of men and women. Urology. 1998;51:206-12.
16. Brierly RD, Hindley RG, McLarty E, Harding DM, Thomas PJ. A prospective controlled quantitative study of ultrastructural changes in the underactive detrusor. J Urol. 2003;169:1374-8.
17. Lee WC, Wu HP, Tai TY, Liu SP, Chen J, Yu HJ. Effects of diabetes on female voiding behavior. J Urol. 2004;172:989-92.
18. Miyazato M, Yoshimura N, Chancellor MB. The other bladder syndrome: underactive bladder. Rev Urol. 2013;15:11-22.
19. Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, et al. Prevalence and Clinical Features of Detrusor Underactivity among Elderly with Lower Urinary Tract Symptoms: A Comparison between Men and Women. Korean J Urol. 2012;53:342-8.
20. van Koeveringe GA, Vahabi B, Andersson KE, Kirschner-Herrmans R, Oelke M. Detrusor underactivity: a plea for new approaches to a common bladder dysfunction. Neurourol Urodyn. 2011;30:723-8.
21. Jiang YH, Lin VC, Liao CH, Kuo HC. International Prostatic Symptom Score-voiding/storage subscore ratio in association with total prostatic volume and maximum flow rate is diagnostic of bladder outlet-related lower urinary tract dysfunction in men with lower urinary tract symptoms. PLoS One. 2013;8:e59176.

Correspondence address:
Jefferson Kalil, MD
Escola de Ciências Médicas,
Universidade Estadual de Campinas – Unicamp,
Rua Tessália Vieira de Camargo, 126,
Cidade Universitária Zeferino Vaz
Campinas, SP, 13083-887, Brasil
Telefone: + 55 19 3521-8863
E-mail: jeffkalil@hotmail.com

ORIGINAL ARTICLE

Vol. 46 (3): 425-433, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0413

Effect of pelvimetric diameters on success of surgery in patients submitted to robot-assisted perineal radical prostatectomy

Mustafa Gurkan Yenice [1], Ismail Yigitbasi [1], Rustu Turkay [2], Selcuk Sahin [1], Volkan Tugcu [1]

[1] University of Health Sciences, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, Istanbul, Turkey; [2] University of Health Sciences, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Radiology, Istanbul, Turkey

ABSTRACT

Objective: Minimally invasive techniques are used increasingly by virtue of advancements in technology. Surgery for prostate cancer, which has high morbidity, is performed with an increasing momentum based on the successful oncological and functional outcomes as well as cosmetic aspects.

Materials and methods: Sixty two patients underwent robot-assisted perineal radical prostatectomy (R-PRP) surgery at our clinic between November 2016 and August 2017. Six pelvimetric dimensions were defined and measured by performing multiparametric magnetic resonance imaging (mpMRI) prior to operation in all patients. In light of these data, we aimed to investigate the effect of pelvimetric measurements on surgery duration and surgical margin positivity.

Results: By using this technique in pelvic area, we observed that measurements only representing surgical site and excluding other pelvic organs had a significant effect on surgery duration, and pelvic dimensions had no significant effect on surgical margin positivity.

Conclusion: In R-PRP technique, peroperative findings and oncological outcomes can vary depending on several variable factors, but although usually not taken into account, pelvimetric measurements can also affect these outcomes. However, there is a need for randomised controlled trials to be conducted with more patients.

ARTICLE INFO

Ismail Yigitbasi
http://orcid.org/0000-0002-1674-6574

Keywords:
Prostatic Neoplasms; Prostatectomy; Perineum

Int Braz J Urol. 2020; 46: 425-33

Submitted for publication:
June 27, 2019

Accepted after revision:
October 13, 2019

Published as Ahead of Print:
December 30, 2019

INTRODUCTION

As the prostate anatomy and distribution of neurovascular bundle (NVB) have been better understood, radical prostatectomy has become increasingly used as part of multimodal treatment to eradicate the disease in local-stage cancer and high-risk prostate cancer (1). While radical prostatectomy results in eradication of disease, open, laparoscopic or robot-assisted radical prostatectomy (RALP) can be performed by considering benefits and side effects of the technique (2). According to literature findings, pelvic dimensions were determined to be an important impact factor in oncological and functional outcomes of surgical methods used. Apical prostate depth is an important impact factor for laparoscopic radical prostatectomy (LRP) and retropubic radical prostatectomy (RRP)

(3). Another important study showed that the pelvic diameter measurements were not predictive of improvement in erectile function in patients underwent RRP (4). Based on the evidence from studies of RALP method, pelvimetric dimensions were proved to be ineffective for surgery duration, amount of bleeding, and recovery of potency and continence at 6-month follow-up of patients underwent this technique (5).

Unlike conventional methods, robot-assisted perineal radical prostatectomy (R-PRP) is performed through perineal approach. In addition, it has many advantages in patients with a history of major abdominal surgery and high body mass index. As this technique is performed below the endopelvic fascia and bladder neck level, anatomy and physiology created by several prior surgeries such as kidney transplantation or intestinal bypass systems for colorectal cancer can be maintained. Tugcu et al. performed this technique in 15 patients and reported that it can be safely performed in terms of oncological and functional outcomes (6). In this study, we aimed to investigate the effect of pelvimetric diameters measured preoperatively by multiparametric magnetic resonance imaging on peroperative findings and postoperative oncological outcomes.

MATERIALS AND METHODS

Based on our database collected prospectively, 62 patients received R-PRP treatment for prostate cancer between November 2016 and August 2017. All mpMRI images were obtained using 3 Tesla MRI machine (Magnetom Verio; Siemens, Erlanger, Germany). Sequences taken were T1-weighted axial and T2-weighted triplanar (axial, sagittal and coronal) and diffusion-weighted images (b values were calculated to be 0, 400, 800, 1400 and 1400). mpMRI did not reveal extraprostatic spread in any of the patients. We performed R-PRP method by placing a gel-port platform on the potential space, which was demarcated by rectourethral muscles and created by open perineal dissection, followed by robotic procedure. All the cases were performed by a single surgeon who has advanced experiences on robotic surgery. In our study, 6 pelvimetric dimensions were measured by an experienced radiologist. The first dimension consists narrowest distances between tips of the ischial spines (ISD) in T2- weighted axial images (Figure-1a). Unlike other techniques in R-PRP, surgery is performed in only minor pelvis with perineal approach. The second dimension is composed angle of the intersection of the straight lines extending from the tuber ischiadicum to the symphysis pubis (ASP) in the T2 weighted sequence coronal images (Figure-1b). We think that this angle represents the minor pelvis. The third dimension is the anteroposterior diameter of pelvic midplane between lower tip of the symphysis pubis and the coccyx representing the pelvic outlet (DPO) (Figure-1c). In other techniques, pelvic inlet and outlet are important because of the operation with abdominal approach, in R-PRP only pelvic outlet is important because technique is performed below endopelvic fascia level. The fourth dimension is the distance of the pelvic midplane from the anterior border of the anus to the apex of the prostate in sagittal images (DAA) (Figure-2a). The fifth dimension is the distance of the pelvic midplane from the anterior border of the anus to anterior border of the centre of seminal vesicles in sagittal images (DSA) (Figure-2b). The sixth dimension is the angle formed by the intersection of the axis passing through the lower and upper tips of the symphysis pubis and the axis intersecting of the seminal vesicles in cranio-caudal line on the sagittal midplane of pelvis (ASS) (Figure-2c). This angle represents the area below the level of endopelvic fascia when the rectum is excluded from the minor pelvis. In addition, prostate volume and body mass index of patients were measured and the effects of results on open perineal procedure time, console time and total operative time, and perioperative findings and postoperative oncological outcomes were examined.

Statistical analysis

Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, maximum). Multiple linear regression analysis was performed to examine the effect of independent variables on continuous dependent variables. Statistical significance level

Figure 1A - Distance of the ischial spines.

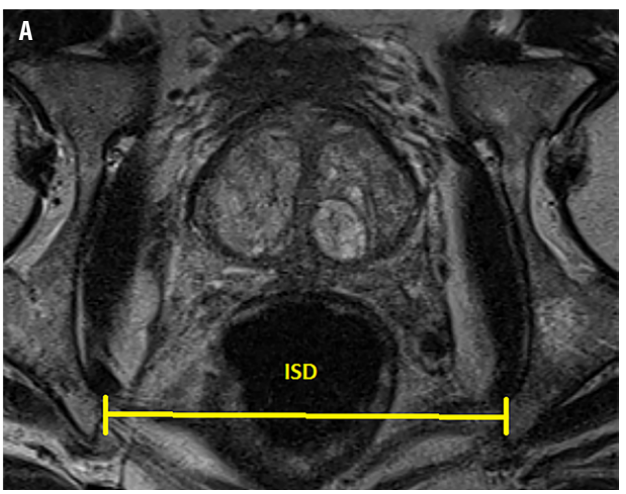


Figure 1B - Angle of symphysis pubis.

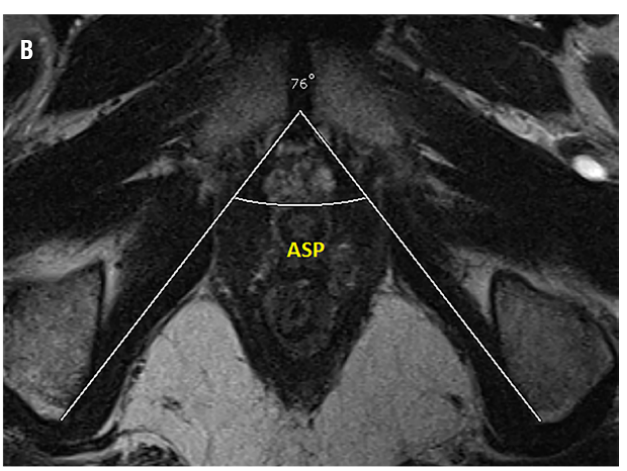


Figure 1C - Distance of pelvic outlet.

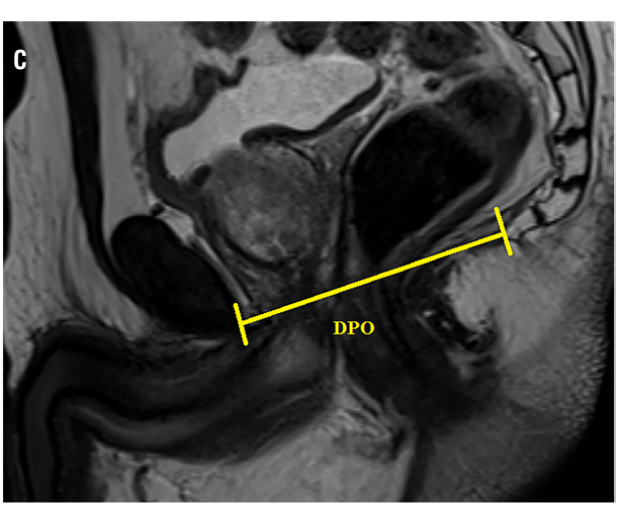


Figure 2a - Distance between prostate apex and anus.

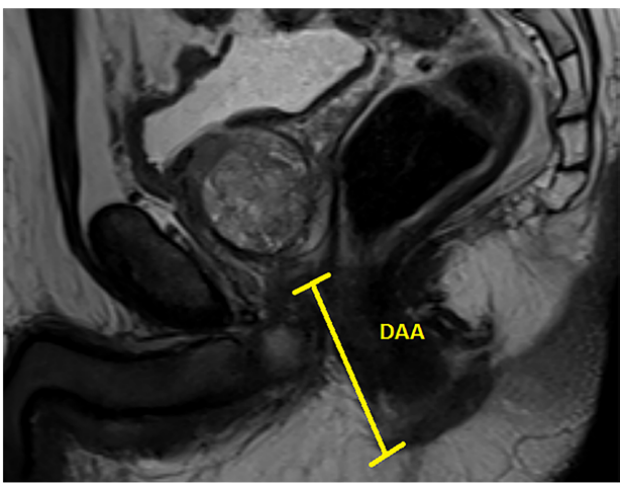


Figure 2b - Distance between seminal vesicles and anus.

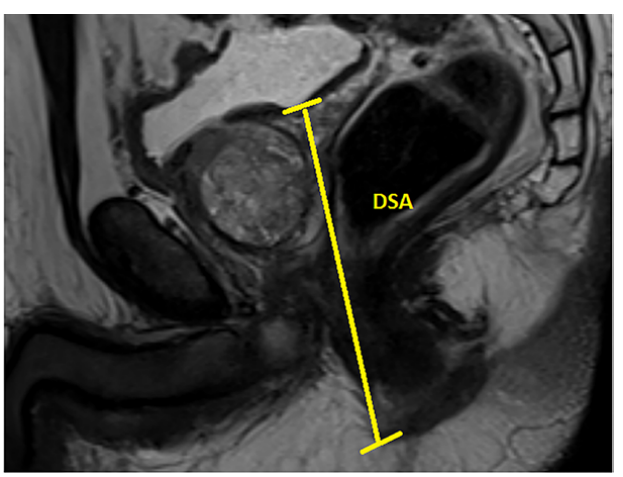
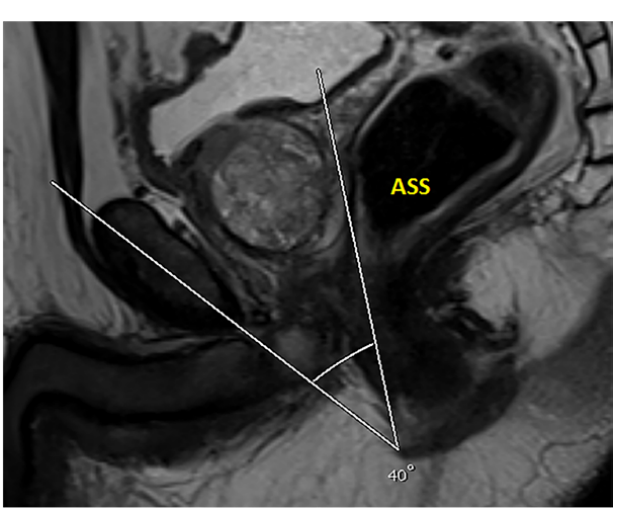


Figure 2C - Angle of symphysis pubis-seminal vesicles.



was considered to be 0.05. Analyses were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; 2013).

Surgical technique

In the first stage, surgery was initiated by performing an open perineal dissection. A potential space was created by extending the dissection into the rectourethral muscle fibres. GelPOINT® (Applied Medical, Rancho Santa Margarita, CA, USA) was placed on this space with the patient on 15-degree Trendelenburg and exaggerated lithotomy position. Three 8mm robotic trocars and one 12mm assistant trocar were placed on gel port. Trocar on 7 o'clock position was used for bipolar robotic arm and robotic trocar on 5 o'clock position was used for scissors and large needle robotic arm. Assistant trocar was placed on 6 o'clock position (Figure-3a). Robot was docked and robot-assisted perineal radical prostatectomy was performed using 3-arm Da Vinci Xi HD Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA). Prostate was released by dissecting lateral prostate lobes starting from apex dissection. Seminal vesicles were completely dissected. Urethra was cut following the dissection starting from dorsal plane. Urethral catheter removed from urethra was clipped with a Hem-o-Lock clip. Urethral catheter to be used for traction was cut below the clips by maintaining the insufflation of balloon. Dorsal veins were released by venous-preserving dissection. Prostatic pedicles were dissected and Hem-o-Lock® Clip (Teleflex Medical, Research Triangle Park, North Carolina, USA) was placed and cut (Figure-3b). Bladder neck was dissected and cut (Figure-3c). After completion of prostatectomy, vesicourethral anastomosis was performed by modified

Figure 3A - Trocar placement and docking for R-PRP.

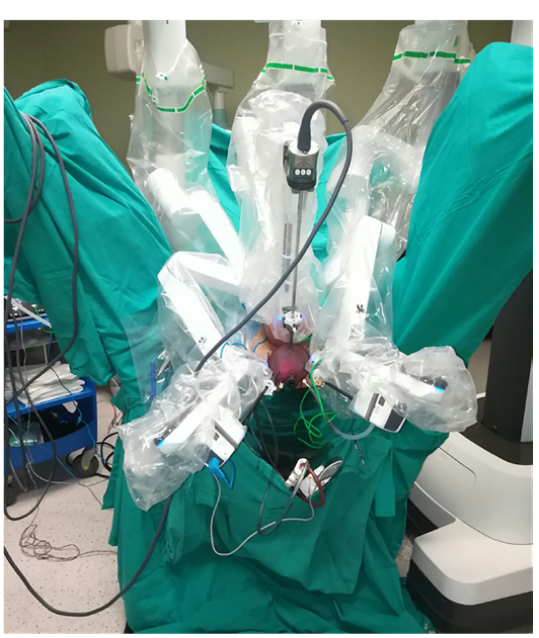


Figure 3B - Dissection of prostatic pedicles.

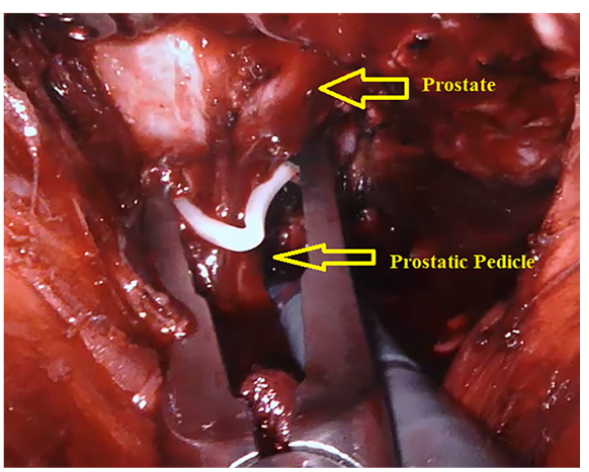
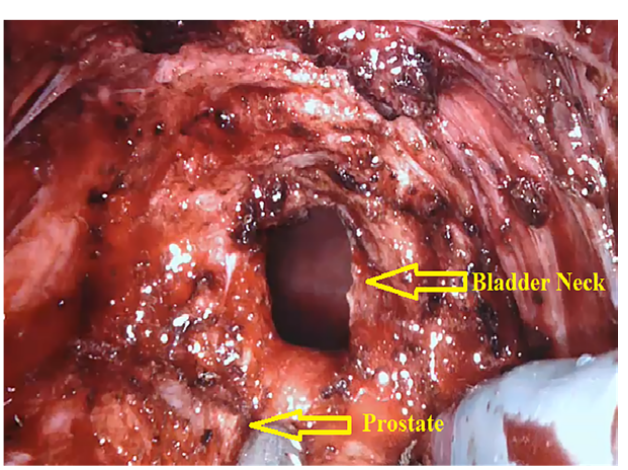
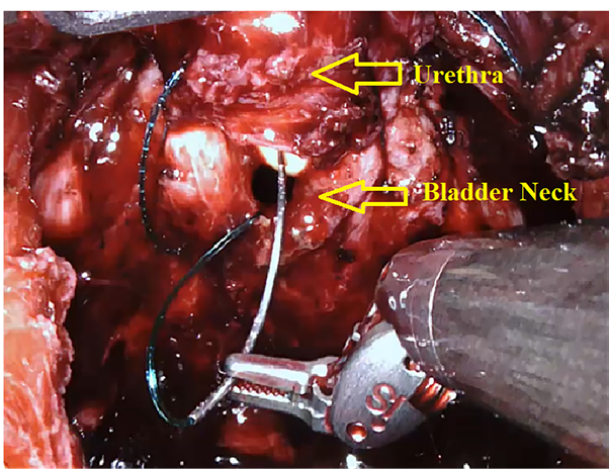


Figure 3C - Dissection of bladder neck.



Van Veltoven technique using 2/4/V-Loc™ (Covidien, Mansfield, MA, ABD) sutures (Figure-3d).

Figure 3D - Vesico-urethral anastomosis in R-PRP.



RESULTS

Patient's preoperative demographics, peroperative and postoperative data and pelvimetric measurement results are summarised in Tables 1, 2, 3 and 4, respectively. Results show that the open perineal dissection time is affected by ASS and DSA dimensions during the first phase of surgery. An inverse proportion was observed with ASS (p=0.004), while a direct proportion was seen with DSA (p=0.013). Open perineal dissection time was increased 0.242-fold with a 1-degree decrease in ASS and 0.277-fold with a 1mm increase in DSA. No significant statistical relationship was observed between other measurements and open perineal dissection time. During the second phase of surgery, console time was observed to be affected inversely proportional to ASP (p=0.024) and ASS (p <0.001) dimensions. Console time was increased 1.040-fold with a 1-degree decrease in ASP and 0.845-fold with a 1-degree decrease in ASS. Total operative time was affected inversely proportional to ASP (p=0.031) and ASS (p <0.001) dimensions. It was increased 1.030-fold with a 1-degree decrease in ASP and 0.875-fold with a 1-degree decrease in ASS. Prostate volume did not cause a change in open perineal dissection time. Body mass index and prostate volume were not observed to have a statistical effect on console time and total operative time. Open perineal dissection time was found to be inversely proportional to body mass index of patient (p=0.038) and increased 0.974-fold with each increment in body mass index. Blood loss

Table 1 - Demographic and the preoperative data.

	r-PRP
Mean age (Range)	63.4 (46-73)
Mean BMI (kg/m^2-Range)	28.5 (24-32)
Mean PSA (ng/mL-Range)	7.35 (3.92-17.3)
Prostate Volume (cc-Range)	69.8 (25-140)
Previous abdominal/Pelvic Surgery	
Yes	40 (64%)
No	22 (36%)
ASA score	
1	5 (4%)
2	54 (87%)
3	5 (8%)
Charlson score	
≤2	58 (89%)
>2	4 (11%)
Clinical stage	
T1c	6 (9%)
T2a	10 (16%)
T2b	18 (29%)
T2c	28 (45%)
Gleason Score	
6	44 (71%)
3+4	18 (29%)

Table 2 - Peroperative data.

	r-PRP
Mean console time (Minute-Range)	96.3 (55-160)
Open perineal dissection time (Minute-Range)	45.4 (30-65)
Mean blood loss (cc-range)	75.8 (40-145)
Anastomosis Time (Minute-Range)	11.8 (10-19)

was observed to be affected inversely proportional to ASP (p=0.024) and ASS (p=0.003), and directly proportional to DSA (p=0.023). Blood loss was increased 1.456-fold with a 1-degree decrease in ASP, 1.758-fold with a 1-degree decrease in ASS and 1.160-fold with a 1-degree increase in DSA (Table-5).

Table 3 - Postoperative Data.

Mean hospitalization (Day-range)	1.92 (1-3)
Mean bladder catheterization time (Day-range)	8.54 (5-12)
Positive surgical margin	(8%)
T2a	0
T2b	2 (3.2%)
T2c	3 (4.8%)

DISCUSSION

Recently defined, R-PRP technique is performed by a different anatomic approach and unlike conventional radical prostatectomy techniques, it causes little to no damage to physiological system created by prior intraabdominal surgeries. It may overcome many difficulties and provides additional advantages in cases where surgical treatment is usually not preferred as a treatment option due to the additional morbidity caused by conventional methods. For example, anatomic problems, intestinal injury risk and dissection of intestinal adhesions to reach the prostate area are the main challenges faced by surgeons in patients with prior history of abdominal surgery. Therefore, serious negative effects can be observed in postoperative oncological and functional outcomes. This technique is also compliant with anatomy

Table 4 - Pelvimetric Dimensions.

Mean distance of the ischial spines (ISD) (mm)	75.1 (49.2-107.1)
Mean angle of symphysis pubis (ASP) (degree)	67.3 (55-77)
Mean distance of pelvic outlet (DPO) (mm)	92.4 (86-112)
Mean distance between prostate apex and anus (DAA) (mm)	52.1 (32.1-70.1)
Mean distance between seminal vesicles and anus (DSA) (mm)	74.1 (55.7-93)
Mean angle of symphysis pubis-seminal vesicles (ASS) (degree)	59.02 (34-86)

Table 5 - Effects of Pelvimetric Dimensions.

AOT	CT	OPDT	EBL	CMP	p value
ISD	0.946	0.806	0.145	0.746	0.148
ASP	0.031	0.024	0.230	0.024	0.412
DPO	0.868	0.930	0.640	0.678	0.618
DAA	0.765	0.912	0.162	0.246	0.112
DSA	0.781	0.548	0.013	0.023	0.092
ASS	<0.001	<0.001	0.004	0.003	0.326
PV	0.428	0.821	0.128	0.164	0.228
BMI	0.816	0.732	0.038	0.326	0.712

ISD = Distance of the ischial spines; **ASP** = Angle of symphysis pubis; **DPO** = Distance of pelvic outlet; **DAA** = Distance between prostate apex and anus; **DSA** = Distance between seminal vesicles and anus; **ASS** = Angle of symphysis pubis-seminal vesicles; **PV** = Prostate volume; **BMI** = Body mass index; **AOT** = All operation time; **CT** = Console time; **OPDT** = Open perineal dissection time; **EBL** = Estimated blood loss; **CMS** = Surgical margin status.

and physiology created by prior surgeries. For example, in patients with a history of surgery such as kidney transplantation, prostate-sparing radical cystectomy and orthotopic urinary diversion and intestinal bypass for malignancy, it maintains the physiology of these surgeries postoperatively. Many surgeons try to maintain the oncological and functional outcomes despite the additional morbidities caused by prior surgeries. Thus, R-PRP provides a great convenience for surgeons in these cases and helps them cope with such issues.

Unlike other methods, this technique is performed with an instrument manoeuvre capability of 540 degrees under the high-resolution image of robotic system at a different compartment in a narrow area. However, there may be some factors that can be considered as limitations of this technique such as different pelvimetric measurements obtained in individual patients. This technique combines open and robotic surgeries and thus, requires a good knowledge on the anatomy of lower abdomen and pelvic floor. Especially during the open perineal dissection phase, rectum and surrounding soft tissue injuries may occur and lead to a process that can cause mortality. Rectum is not completely dissected during open perineal dissection phase, but mostly dissected and completely separated from prostate during robotic surgery phase. Korman et al. reported a rectal injury rate of 1-11% in a series of open perineal radical prostatectomy, Amorim et al. reported a rectal injury risk of 2.2-2.4% in laparoscopic extraperitoneal radical prostatectomy and Tewari et al. reported a rectal injury rate of 0.5-1.5% in a series of robotic radical prostatectomy (7-9). No rectal injury was observed in our series of R-PRP. Although it is believed that surgeons may experience some difficulties with the narrowing of pelvic area, good knowledge on pelvic and perineal anatomy, high-resolution images of robotic system and high level of experience in robotic surgery play important roles in success of this surgery.

According to study conducted by Violette PD, blood loss, preoperative PSA, robot malfunction and prostate volume are independent factors that prolong the operative time in RALP. In addition, mean operative time was reported to be 187 minutes (10). While completion of learning curve by the surgeon is another important factor, prior history of surgery and BMI are other factors that should be considered. Our study included 62 cases and we believe that this number of cases is sufficient for completion of learning curve. Mean operative time in our study can be considered acceptable when compared to other techniques. When all these data are ignored, pelvimetric dimensions can also be suggested as independent predictive factors for R-PRP. In result of their evaluation on prostate volume in terms of RALP, Hong et al. reported that the surgery duration, but not the pelvimetric dimensions, can be considered as an independent predictor (11). We believe that the pelvimetric measurement can have a high degree of significance if it covers surgical site only and excludes other organs in order to be considered as a predictive factor for the effect of pelvimetric dimensions on operative time. We assessed the operation in 3 phases individually when evaluating our technique based on the pelvimetric measurements. These were open perineal dissection, console time and total operative time. Among our pelvimetric measurements, ASS was found to be statistically significant for duration of all surgical procedures and each surgical phase became shorter individually with the increase in ASS. We believe that ASS significantly affects each phase as it only represents the surgical site where operation was performed. Our technique is performed in front of the rectum below the bladder neck and endopelvic fascia level using perineal approach. Therefore, while pelvic outlet can be a predictor, pelvic inlet cannot be a predictive factor because it is located completely outside the surgical site. ASP angle was found to be significant for total operative time and console time but with a lesser statistical significance compared to ASS since ASP angle included rectum and surrounding soft tissues. While DSA and BMI affect open perineal dissection time, these parameters do not affect other procedure times. As perineal approach was adopted, DSA particularly represents the mean length of prostate depth. This can be considered as a cause of its effect on open perineal dissection time.

Many studies revealed that the parameters such as BMI, prostate volume, intraabdominal pressure and patient's age at the time of robotic or laparoscopic radical prostatectomy are predictive

factors for blood loss. Apart from these, it can be suggested that the pelvimetric measurements play a role in blood loss. Hong et al. reported that pelvimetric measurements do not affect the amount of blood loss in RALP operation but prostate volume is a predictive factor (11). According to data of our study, ASS, ASP and DSA measurements have an effect on blood loss. Surgical site becomes broader with the increase in ASS and ASP and performance of radical prostatectomy becomes easier with R-PRP technique. Bleeding can be controlled more effectively with the increased manoeuvre capability at this broadened area. With the increase in DSA, operation is performed at a deeper site in perineal area, which results in increased levels of blood loss. Based on the literature, blood loss is known to be reduced in RALP technique compared to other methods. Consistent with the literature, mean blood loss during RALP surgery was measured to be 190cc in our study (12, 13). For R-PRP technique, positive pressure on a narrow area, high-level robotic optical resolution and lack of need for dorsal vein complex dissection and ligation below the endopelvic fascia level are among the most important factors that reduce blood loss.

In the literature, Matikainen MP et al. reported that apical depth is an independent predictive factor for positive apical surgical margin (14). Tozawa et al. reported the rate of surgical margin as 26% in their series of RALP (15). Positive surgical margin rates of our series are consistent with literature. We determined that the pelvimetric diameter is not an independent predictive factor for surgical margin positivity in R-PRP technique. We believe that R-PRP can be safely performed without increasing surgical margin positivity regardless of pelvimetric measurements in localised prostate cancer.

The technique we performed is a novel and developing method. Some of the dimensions evaluated were overall pelvimetric dimensions, while others were dimensions defined by us to represent the surgical site only. We showed that some pelvimetric measurements can be considered as predictive factors for surgery duration. Number of patients can be considered as the limitation of this study.

CONCLUSIONS

In R-PRP technique, peroperative findings and oncological outcomes can vary depending on several variable factors, but although usually not taken into account, pelvimetric measurements can also affect these outcomes. However, there is a need for randomised controlled trials to be conducted with large series of patients.

ABBREVIATIONS

R-PRP = Robot-assisted radical perineal prostatectomy
mpMRI = Multiparametric magnetic resonance imaging
NVB = Neurovascular bundle
RALP = robot-assisted radical prostatectomy
LRP = Laparoscopic radical prostatectomy
RRP = Retropubic radical prostatectomy
ISD = Distance of the ischial spines
ASP = Angle of symphysis pubis
DPO = Distance of pelvic outlet
DAA = Distance between prostate apex and anus
DSA = Distance between seminal vesicles and anus
ASS = Angle of symphysis pubis-seminal vesicles
BMI = Body mass index

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology. 2005;66(5 Suppl):83-94.
2. Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet. 2016;388:1057-1066. Erratum in: Lancet. 2017;389:e5.
3. Matikainen MP, von Bodman CJ, Secin FP, Yunis LH, Vora K, Guillonneau B, et al. The depth of the prostatic apex is an independent predictor of positive apical margins at radical prostatectomy. BJU Int. 2010;106:622-6.

4. von Bodman C, Matikainen MP, Favaretto RL, Matsushita K, Mulhall JP, Eastham JA, et al. Pelvimetric dimensions do not impact upon nerve sparing or erectile function recovery in patients undergoing radical retropubic prostatectomy. J Sex Med. 2011;8:567-74.
5. Hong SK, Lee ST, Kim SS, Min KE, Hwang IS, Kim M, et al. Effect of bony pelvic dimensions measured by preoperative magnetic resonance imaging on performing robot-assisted laparoscopic prostatectomy. BJU Int. 2009;104:664-8.
6. Tuğcu V, Akça O, Şimşek A, Yiğitbaşı İ, Şahin S, Taşçı Aİ. Robot-assisted radical perineal prostatectomy: first experience of 15 cases. Turk J Urol. 2017;43:476-83.
7. Korman HJ, Mulholland TL, Huang R. Preservation of fecal continence and bowel function after radical perineal and retropubic prostatectomy: a questionnaire-based outcomes study. Prostate Cancer Prostatic Dis. 2004;7:249-52.
8. Amorim GL, Cruz GM, Veloso DF, Kartabil JD, Vieira JC, Alves PR. Comparative analysis of radical prostatectomy techniques using perineal or suprapubic approach in the treatment of localized prostate cancer. Einstein (Sao Paulo). 2010;8:200-4.
9. Tewari A, Sooriakumaran P, Bloch DA, Seshadri-Kreaden U, Hebert AE, Wiklund P. Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy. Eur Urol. 2012;62:1-15.
10. Violette PD, Mikhail D, Pond GR, Pautler SE. Independent predictors of prolonged operative time during robotic-assisted radical prostatectomy. J Robot Surg. 2015;9:117-23.
11. Hong SK, Lee ST, Kim SS, Min KE, Hwang IS, Kim M, et al. Effect of bony pelvic dimensions measured by preoperative magnetic resonance imaging on performing robot-assisted laparoscopic prostatectomy. BJU Int. 2009;104:664-8.
12. Ehieli EI, Howard LE, Monk TG, Ferrandino MN, Polascik TJ, Walther PJ, et al. Effect of positive end-expiratory pressure on blood loss during retropubic and robot-assisted laparoscopic radical prostatectomy. Int J Urol. 2016;23:674-8.
13. Berge V, Berg RE, Hoff JR, Wessel N, Diep LM, Karlsen SJ, et al. A prospective study of transition from laparoscopic to robot-assisted radical prostatectomy: quality of life outcomes after 36-month follow-up. Urology. 2013;81:781-6.
14. Matikainen MP, von Bodman CJ, Secin FP, Yunis LH, Vora K, Guillonneau B, et al. The depth of the prostatic apex is an independent predictor of positive apical margins at radical prostatectomy. BJU Int. 2010;106:622-6.
15. Tozawa K, Yasui T, Umemoto Y, Mizuno K, Okada A, Kawai N, et al. Pitfalls of robot-assisted radical prostatectomy: a comparison of positive surgical margins between robotic and laparoscopic surgery. Int J Urol. 2014;21:976-9.

Correspondence address:
Ismail Yigitbasi, MD
Department of Urology,
University of Health Sciences, Istanbul Bakirkoy Dr.
Sadi Konuk Training and Research Hospital
Istanbul, Turkey
Zuhuratbaba Mh. Tevfik Saglam Cd. No:11
Bakirkoy, Istanbul, Turkiye
Telephone: + 90 551 414 19 22
Email: ismail.yigitbasi1@saglik.gov.tr

EDITORIAL COMMENT

Vol. 46 (3): 434-435, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0413.1

Editorial Comment: Effect of pelvimetric diameters on success of surgery in patients submitted to robot-assisted perineal radical prostatectomy

Gilberto J. Rodrigues [1], Rafael F. Coelho [1]

[1] *Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo – USP, São Paulo, SP, Brasil*

COMMENT

The outcomes of Radical prostatectomy (RP), regardless of the surgical approach, play an important role on patients' quality of life, mainly due its impact on urinary and sexual function. These outcomes are dependent on multiple factors including patient's anatomy, age, comorbidities, tumor staging, surgeon's experience, nerve sparing approach among others (1-5). Several statistical models have been published trying to predict functional and oncologic outcomes of RP based on patients' factors and perioperative parameters; these models seek to optimize preoperative counseling and patient selection for RP. However, the outcomes of RP are widely variable and conflicting results were reported with regards the importance of each factor as an independent predictor of surgical outcomes (6-11). The truth is that perioperative, functional and oncological results of RP are far more difficult to estimate, and even unknown factors may play an important role on final outcomes. Thus, in daily clinical practice, those prediction models must be cautiously interpreted and shouldn't be used as a unique tool in patients counseling or to select a specific surgical approach.

Perineal prostatectomy (RPP) was the first and oldest surgical technique described for prostate cancer treatment, progressively replaced by retropubic prostatectomy (RRP) after the introduction and standardization of the nerve-sparing technique by Walsh (12, 13). As technology and surgical techniques evolved, minimally invasive surgery emerged with laparoscopic (LRP) and robotic-assisted prostatectomy (RARP) presenting shorter length of stay, minimal blood loss and potentially better functional outcomes (14, 15). Recently, RRP was adapted to robotic-assisted platform (P-RARP) and it has been described as an option in patients with previous multiple abdominal surgeries, who presents abdominal wall defect with a mesh, obese or transplanted kidney patients, for example (16, 17). However, the real benefits of this approach in terms of surgical outcomes are yet to be proven. Despite the quite interesting findings described by Yenice at al. (18) in the current study, correlating pelvimetric measurements and operative time (but not with positive surgical margins), this findings happens to be just one more of those inconsistent predictive models with controversial results compared to other series (19, 20) and must have minimal impact on the final decision.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Chen J, Chu T, Ghodoussipour S, Bowman S, Patel H, King K, et al. Effect of surgeon experience and bony pelvic dimensions on surgical performance and patient outcomes in robot-assisted radical prostatectomy. BJU Int. 2019;124:828-35.
2. Ko WJ, Truesdale MD, Hruby GW, Landman J, Badani KK. Impacting factors for recovery of erectile function within 1 year following robotic-assisted laparoscopic radical prostatectomy. J Sex Med. 2011;8:1805-12.
3. Hung AJ, Chen J, Jarc A, Hatcher D, Djaladat H, Gill IS. Development and Validation of Objective Performance Metrics for Robot-Assisted Radical Prostatectomy: A Pilot Study. J Urol. 2018;199:296-304.
4. Antonelli A, Palumbo C, Noale M, Porreca A, Maggi S, Simeone C, et al. Impact of Surgical Approach on Patient-Reported Outcomes after Radical Prostatectomy: A Propensity Score-Weighted Analysis from a Multicenter, Prospective, Observational Study (The Pros-IT CNR Study). Urol Int. 2019;103:8-18.
5. Lardas M, Liew M, van den Bergh RC, De Santis M, Bellmunt J, Van den Broeck T, et al. Quality of Life Outcomes after Primary Treatment for Clinically Localised Prostate Cancer: A Systematic Review. Eur Urol. 2017;72:869-85.
6. Favorito LA. Age and Body Mass Index: the most important factors of urinary and erectile function recovery after robotic assisted radical prostatectomy. Int Braz J Urol. 2019;45:653-4.
7. Kanehira M, Takata R, Ishii S, Ito A, Ikarashi D, Matsuura T, et al. Predictive factors for short-term biochemical recurrence-free survival after robot-assisted laparoscopic radical prostatectomy in high-risk prostate cancer patients. Int J Clin Oncol. 2019;24:1099-104.
8. Moureaux C, Boucaud-Maitre D, Brureau L, Gourtaud G, Senechal C, Roux V, et al. Pelvimetrics measures as predictives factors of positives surgical margins after robot-assisted laparoscopic prostatectomy. Prog Urol. 2018;28:906-14.
9. Matikainen MP, von Bodman CJ, Secin FP, Yunis LH, Vora K, Guillonneau B, et al. The depth of the prostatic apex is an independent predictor of positive apical margins at radical prostatectomy. BJU Int. 2010;106:622-6.
10. Coelho RF, Cordeiro MD, Padovani GP, Localli R, Fonseca L, Pontes J Júnior, et al. Predictive factors for prolonged hospital stay after retropubic radical prostatectomy in a high-volume teaching center. Int Braz J Urol. 2018;44:1089-105.
11. Ko YH, Coelho RF, Chauhan S, Sivaraman A, Schatloff O, Cheon J, et al. Factors affecting return of continence 3 months after robot-assisted radical prostatectomy: analysis from a large, prospective data by a single surgeon. J Urol. 2012;187:190-4.
12. Young HH. The early diagnosis and radical cure of carcinoma of the prostate. Being a study of 40 cases and presentation of a radical operation which was carried out in four cases. 1905. J Urol. 2002;167(2 Pt 2):939-46; discussion 947.
13. Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. Prostate. 1983;4:473-85.
14. Ilic D, Evans SM, Allan CA, Jung JH, Murphy D, Frydenberg M. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. Cochrane Database Syst Rev. 2017;9:CD009625.
15. Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet. 2016;388:1057-66.
16. Laydner H, Akça O, Autorino R, Eyraud R, Zargar H, Brandao LF, et al. Perineal robot-assisted laparoscopic radical prostatectomy: feasibility study in the cadaver model. J Endourol. 2014;28:1479-86.
17. Ekşi M, Çolakoğlu Y, Tuğcu V, Sahin S, Simsek A, Evren İ, et al. Robot Assisted Radical Perineal Prostatectomy; Review of 95 Cases. BJU Int. 2020;27. [Epub ahead of print]
18. Yenice MG, Yigitbasi I, Turkay R, Sahin S, Tugcu V. Effect of pelvimetric diameters on success of surgery in patients submitted to robot-assisted perineal radical prostatectomy. Int Braz J Urol. 2020;46: 425-33.
19. Moureaux C, Boucaud-Maitre D, Brureau L, Gourtaud G, Senechal C, Roux V, et al. Pelvimetrics measures as predictives factors of positives surgical margins after robot-assisted laparoscopic prostatectomy. Prog Urol. 2018;28:906-14.
20. Matikainen MP, von Bodman CJ, Secin FP, Yunis LH, Vora K, Guillonneau B, et al. The depth of the prostatic apex is an independent predictor of positive apical margins at radical prostatectomy. BJU Int. 2010;106:622-6.

ARTICLE INFO

Rafael F. Coelho
https://orcid.org/0000-0003-3835-0789

Int Braz J Urol. 2020; 46: 434-5

Submitted for publication:
January 25, 2020

Accepted after revision:
February 10, 2020

Rafael F. Coelho, MD

Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo – USP
Av. Dr. Arnaldo, 455 - Cerqueira César
São Paulo, SP, 01246-903, Brasil
E-mail: coelhouro@yahoo.com.br

ORIGINAL ARTICLE

Vol. 46 (3): 436-443, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0453

Effects of spongioplasty on neourethral function following hypospadias repair: an experimental study in rabbits

Linhai Xie [1], Yaqi Xi [1], Xue Zhang [1], Hongbiao Ding [1], Senkai Li [2]

[1] Department of Plastic Surgery, First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, China; [2] Hypospadias Treatment Center, Plastic Surgery Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

ABSTRACT

Purpose: Spongioplasty (mobilization and midline approximation of the two branches of the bifid dysplastic distal corpus spongiosum) can form a covering layer for the neourethra to prevent urethrocutaneous fistula in hypospadias repair surgery. However, it remains unclear whether spongioplasty affects neourethral function. The objective of this study was to compare neourethral function after hypospadias repair with and without spongioplasty.

Materials and Methods: Fourteen congenital hypospadiac New Zealand male rabbits were randomly allocated into two groups, seven animals underwent Duplay hypospadias repair and spongioplasty (experimental group), while seven underwent Duplay surgery alone (control group). Functional differences between groups were assessed by comparing neourethral compliance and flow rate. Two months after surgery, in vivo neourethral compliance was assessed by measuring intraluminal pressure with a digital pressure meter of an isolated neourethral segment, following progressive distension with 1, 2, and 3mL of air. Penises were harvested for uroflowmetry test using a simple device.

Results: Postoperatively, fistula developed in one and zero rabbits in the control and experimental groups, respectively. Mean pressures tended to be higher in the experimental group than in the control group (82.14 vs. 69.57, 188.43 vs. 143.26, and 244.71 vs. 186.29mmHg for 1, 2, and 3mL of air, respectively), but the difference was not statistically significant. Mean flow rates also did not significantly differ between the experimental and control groups (2.93mL/s vs. 3.31mL/s).

Conclusion: In this congenital rabbit model, no obvious functional differences were found between reconstructed urethras after hypospadias repair with and without spongioplasty.

ARTICLE INFO

Linhai Xie
http://orcid.org/0000-0002-7290-4733

Keywords:
Urethra; Fistula; Hypospadias

Int Braz J Urol. 2020; 46: 436-43

Submitted for publication:
July 11, 2019

Accepted after revision:
October 11, 2019

Published as Ahead of Print:
December 15, 2019

INTRODUCTION

Urethrocutaneous fistula is one of the most common complications following hypospadias repair. To prevent fistula formation, various tissues (e.g., dartos, de-epithelialized penile skin flap, tunica vaginalis, and corpus spongiosum) have been used as protective layers for the neourethra. Fibrous tissues located on both sides of the urethral plate are known as two branches of the bifid dysplastic corpus spongiosum (in some patients they may persist as healthy, well formed pillars of erectile tissues), in recent years, the use of these tissues in spongioplasty, covering the neourethra alone or

with the aid of other tissue layers, has been shown to satisfactorily reduce the fistula rate (1-5). However, the effect of spongioplasty on neourethral function remains unclear. We hypothesized that spongioplasty would cause the neourethra to become thinner and less elastic, due to poor elasticity of the dysplastic spongiosum, resulting in worsened function.

Functional evaluation of the neourethra after hypospadias repair is mainly based on uroflowmetry, more comprehensive assessment requires more complex and intrusive examinations, such as impedance planimetry. However, a simple and effective method has been reported in a rabbit model by Jesus et al., this method measures neourethral compliance based on the intraluminal pressure of an isolated neourethral segment following progressive distension with air using a tensiometer (6). The development of the rabbit penis and urethra are homologous to those processes in humans, and rabbit hypospadias can be induced by 5α-reductase inhibitors (7), thus, in the present study, we evaluated neourethral function following hypospadias repair with and without spongioplasty in a rabbit model of congenital hypospadias.

MATERIALS AND METHODS

Rabbit model

A rabbit model of congenital hypospadias was established by feeding finasteride to pregnant New Zealand White rabbits. The study group consisted of 14 male hypospadiac rabbits of similar age (3 months) and weight (2.25-2.65kg), selected from among 22 rabbits with congenital hypospadias. For all rabbits, the urethral meatus was located at the middle third of the penis. All rabbits were kept in individual cages with a standard rabbit diet, water ad libitum, and routine care. The investigation was approved by our university's animal care and use committee (Approval Number: 201631).

Experimental design

The rabbits were randomly allocated into two equal groups. In experimental group (G1), both Duplay urethroplasty and spongioplasty were performed, whereas only Duplay urethroplasty was performed in control group (G2).Two months after surgery, rabbits were anesthetized for macroscopic and functional evaluation, they were then sacrificed under general anesthesia and their penises were harvested. All measurements were made by a single investigator (not the surgeon), who was blinded to the grouping of the rabbits.

Surgical techniques

All operations were performed under general anesthesia. In group G1, after classic Duplay urethroplasty over a 10Fr silicone catheter, spongioplasty was performed as follows: two branches of the corpus spongiosum were dissected in a lateral to medial manner from the tunica albuginea carefully, the left branch was flipped toward right and sutured to the right side of the neourethral suture line, while the right branch was flipped and sutured in the opposite manner. Hence, the three suture lines did not overlap. Wound coverage was performed using penile skin flaps on both sides, one flap was partially de-epithelialized and moved across the midline, then sutured under the contralateral skin, such that it served as another waterproof layer to cover the neourethra (Figure-1). In group G2, after urethroplasty was completed, the superficial fascia was sutured to cover the neourethral suture line (this procedure was not performed in Group G1) and spongioplasty was not performed, the remaining procedures were identical to those in group G1. No dressing or stent was left in place in either group.

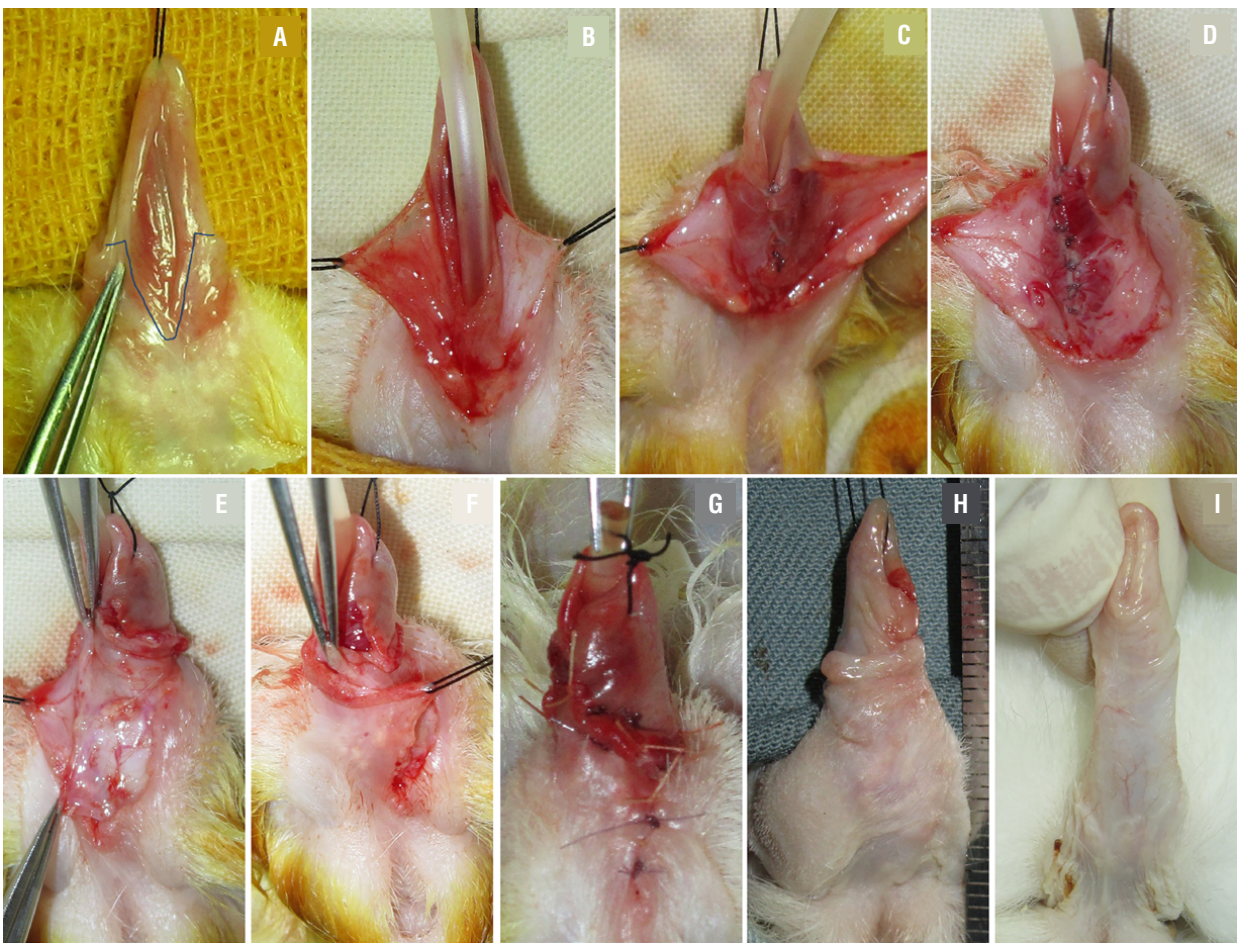
Macroscopic evaluation

Under anesthesia, penile and meatal shape were observed, and fistula presence was assessed by injecting water into the urethra while blocking the proximal urethra. After the rabbits had been sacrificed, one animal from each group was perfused with red and blue emulsions via the abdominal aorta and posterior vena cava intubation, respectively. After 24 hours, the penises were harvested for anatomical observation.

Neourethral compliance examination

Jesus et al. reported a simple and effective method for urethral compliance measurement (6),

Figure 1 - Experimental procedure (Duplay & spongioplasty).



A) preoperative; **B)** skin dissection; **C)** urethroplasty; **D)** spongioplasty; **E)** de-epithelialized penile skin flap; **F)** skin closure; **G)** operation completed; **H)** two months after surgery; **I)** normal penis of 5 month old male rabbit.

we completed this part using their method. Under anesthesia and with the urethra in situ, the urethra was ligated at the level of the penile root and a 10Fr silicone catheter was inserted through the meatus, then, the distal urethra was ligated at exactly 3cm distally from the first ligation, such that an isolated urethral segment was formed (this primarily consisted of neourethra). The catheter tip was placed at the middle of the segment, and its distal end was connected to a digital pressure meter and a syringe through a three-way connector. When air was injected into the segment through the syringe, the intraluminal pressure was transmitted to the pressure meter. The segment was distended with 1, 2, and 3mL of air (with an interval of 5-10 seconds between injections, until the pressure had stabilized), and intraluminal pressures were measured.

Uroflowmetry

Uroflowmetry was performed in fresh urethral segments using a passive flow rate protocol developed by Leslie et al. (8). Briefly, a 50mL syringe was connected with an intravenous line, after it had been filled with water, the system was vertically fixed on the wall to form a 50cm water column (Figure-2). After compliance examination, the same 3cm urethral segment was harvested, its proximal end was sutured to a tube and connected to the end of the intravenous line. The mean flow rate was determined by dividing the amount of water (50mL) by the time required to empty the system.

Statistical analysis

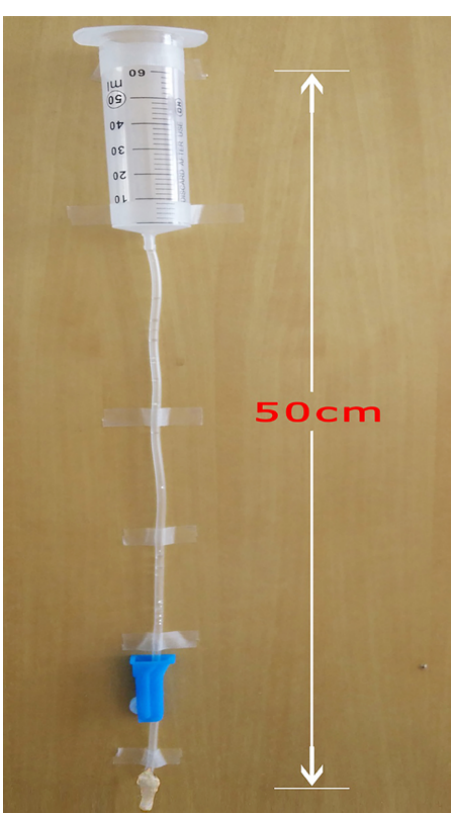
Statistical analysis was performed using SPSS Statistics software (version 17.0, SPSS Inc., Chicago, IL, USA). Data that demonstrated a normal distribution were expressed as the mean and standard deviation. t-tests were used to compare uroflowmetry data between the two groups. Compliance differences between the two groups were compared by analysis of variance of the repeated measurement data. Differences with P <0.05 were considered to be statistically significant.

RESULTS

Surgical results

Spongioplasty was successfully performed in each animal, the mean operating time in group G1 was 100min. (90-120min.), while the mean operating time in group G2 was 70min. (50-80min.). All animals survived until the scheduled sacrifice date and voided spontaneously throughout the study period, no signs of infection or flap necrosis were found postoperatively. Mild rupture of the distal ventral incision (approximately 3mm) occurred in one rabbit in group G1, this healed within 2 weeks.

Figure 2 - A simple flow rate device.



Macroscopic appearance

The meatus was located in a nearly normal position in all rabbits, except the rabbit with the ruptured incision. The prepuce ring was intact and the urethra could be easily calibrated using a 10Fr catheter, indicating that no obvious strictures had formed. A needle size fistula was found in one rabbit in group G2, located near the meatus. Significant differences were observed in the morphology of the corpus cavernosum between the perfusion specimens of the two groups. In group G1, the ventral side of the neourethra was covered by thick spongiosum tissue, the two branches of the bifurcated urethral spongiosum were nearly integrated, with spongiosum absent only near the meatus. In group G2, there was considerable distance between the two branches, the entire ventral neourethral wall was thin and translucent, and the intraluminal catheter could be observed. (Figure-3)

Neourethral compliance

All animals were successfully tested and the results are shown in Table-1, intraurethral pressure was proportional to the volume of injected air. The mean pressure of group G1 was slightly higher than that of group G2, but this difference was not statistically significant.

Uroflowmetry

One rabbit was randomly selected from each group for perfusion and did not undergo uroflowmetry examination. The remaining rabbits were all successfully tested and the results are shown in Table-2, there were no significant differences in uroflowmetry between the two groups.

DISCUSSION

The use of well-vascularized tissue as a protective intermediate layer between the neourethra and the skin is considered an effective measure to prevent urinary fistula, and various tissues

Figure 3 - Corpus spongiosum of experimental (A) and control group (B).

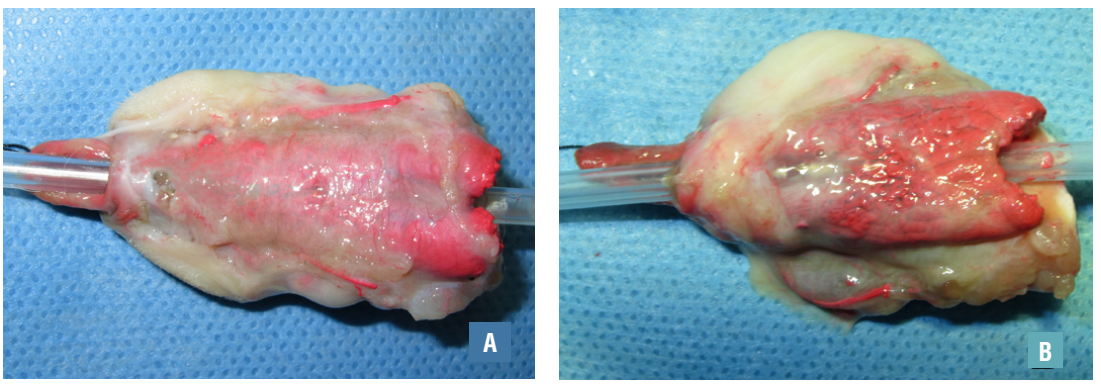


Table 1 - Intraluminal pressures generated by air injection.

Volume of air	Group	N	Pressure (x±s, mmHg)
1mL	G1	7	82.14±16.77
	G2	7	69.57±13.34
2mL	G1	7	188.43±45.52
	G2	7	143.26±30.55
3mL	G1	7	244.71±61.44
	G2	7	186.29±44.04
			F=4.11, P=0.0654

Table 2 - Flow rate results.

Group	N	Folw speed(x±s, mL/s)
G1	6	2.93±0.36
G2	6	3.31±0.59
		t=1.35, *P*=0.2053

(e.g., dartos, de-epithelialized penile skin flap, tunica vaginalis, and corpus spongiosum) have been used (9-12). In 2000, Beaudoin and Yerkes first reported the separation of two branches of the bifurcated urethral spongiosum, which were combined and then used to cover the ventral side of the new urethra, this procedure was termed "spongioplasty" (13, 14). Subsequently, there have been many reports of the use of bifurcated spongiosum (alone or in combination with other tissue layers) as a healthy intermediate tissue layer for use in urethroplasty. It is well-vascularized, robust, and can be conveniently harvested, it is also considered to be physiologically appropriate for use as a protective layer of the neourethra, such that it may aid in the natural propulsion of urine and semen (2, 15, 16). Spongioplasty can reduce suture tension during urethroplasty, and increases the tissue thickness of the ventral penis, thus helping to reduce fistula rate (17). However, it has not yet been reported whether spongioplasty affects neourethral function.

We hypothesized that the combination of two branches of the bifurcated spongiosum may compress or reduce the new urethra due to suture tension, thus modifying its effective diameter, moreover, we hypothesized that this approach may limit urethral expansion because of its fibrous content and poor elasticity, thereby producing unsatisfactory urodynamics. Therefore, we assessed urinary flow rate, urethral diameter, and compliance for comparison of functional differences between experimental and control urethras.

In previous studies, most investigators have employed uroflowmetry to evaluate neourethral function following hypospadias repair; it is considered to be a direct reflection of function, and the flow rate in patients after repair is lower than that in normal controls (8, 18, 19). According to Poiseuille's law ($Q=\pi r^4\Delta P/8\mu L$; where Q=flow, r=radius of pipe, ΔP=pressure difference, μ=viscosity of liquid, and L=length of pipe), the urethral radius has the greatest impact on flow. We examined isolated urethral segments of equal length, and the pressure difference (ΔP, 50cm water column), viscosity of water (μ), and urethral length (L) were fixed, urethral diameter was the only variable in the formula. The difference in flow rate reflected the difference in urethral diameter. Because there was no statistical difference in the flow rate between the two groups, we inferred that there was no significant difference in urethral diameter between the two groups.

Compliance describes the resistance of an elastic organ to undergo deformation by an external force, in particular, highly compliant organs require lower pressure to undergo deformation. In a tubular structure such as the urethra, increased compliance and elasticity indicate that the diameter of the urethra is more likely to increase during urination, thus reducing the resistance of flow (R, $R=8\mu L/\pi r^4$) and increasing the flow rate. Jesus found that the reconstructed urethra has lower compliance than the normal urethra (6), which may explain why many patients have abnormal uroflowmetry results without obvious urethral strictures. We examined the compliance of the neourethra by measuring the intraurethral pressure generated by injection of fixed volumes of air (greater pressure means worse compliance), and found that there was no significant difference in pressure between the two groups. Since the two groups also showed no significant differences in neourethral diameter (10Fr), or in the results of uroflowmetry, we concluded that the difference in compliance between the two groups was not significant.

The development of the rabbit penis and urethra is similar to that observed in humans (e.g., the process by which the urethral plate curls to form the urethra), and the size of the rabbit penis is convenient for surgical manipulation, therefore, the rabbit is an ideal model for the investigation of hypospadias repair. This study used a rabbit model of drug-induced congenital hypospadias, which is superior to the rabbit model of surgically produced hypospadias. Because there are many differences between the normally developed urethra and the hypospadiac urethral plate (e.g., anatomical and biomechanical characteristics, elasticity, and wound healing), which limit the applicability of the surgically produced hypospadias model (20). These differences were especially important in the present study.

No fistulas developed in the experimental group in this study, whereas one rabbit in the control group (14.29%) developed fistula. Postoperative anatomical observation showed the protective effect of spongioplasty on the neourethra. This suggests that spongioplasty may aid in fistula prevention, and has no significant impact on neourethral function (i.e., flow rate and urethral compliance). In addition, we did not evaluate a physiological urethral segment in this study, however, the reunited corpus spongiosum may aid with urethral voiding in vivo.

This study had a few notable limitations. Because rabbits with similar weight and hypo-

spadias classification are difficult to obtain, our sample size was relatively small, which may have affected the generalizability of the findings. In addition, uroflowmetry was performed after compliance assessment (due to limited sample size), therefore the tested urethra had been expanded, which inevitably affected the uroflowmetry results, however, urethras of both groups were equally affected, so this may not have greatly influenced our conclusions.

CONCLUSIONS

In this congenital rabbit model, spongioplasty is surgically feasible and helps prevent fistula, moreover, it had no significant effect on neourethral compliance or flow rate, compared with these parameters in rabbits who had not undergone spongioplasty. Our results suggest that spongioplasty could form an effective protective layer for the neourethra without impairing its function.

FINANCIAL SUPPORT

Study is supported by the project funded under the National Natural Science Foundation of China (General Program). Grant No.: 81560115.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bilici S, Sekmenli T, Gunes M, Gecit I, Bakan V, Isik D. Comparison of dartos flap and dartos flap plus spongioplasty to prevent the formation of fistulae in the Snodgrass technique. Int Urol Nephrol. 2011;43:943-8.
2. Bhat A, Sabharwal K, Bhat M, Saran R, Singla M, Kumar V. Outcome of tubularized incised plate urethroplasty with spongioplasty alone as additional tissue cover: A prospective study. Indian J Urol. 2014;30:392-7.
3. Ekinci S, Çiftçi AÖ, Karnak İ, Şenocak ME. Eccentric circummeatal based flap with limited urethral mobilization: An easy technique for distal hypospadias repair. J Pediatr Urol. 2016;12:116.e1-6.
4. Özbey H, Etker Ş. Hypospadias repair with the glanular-frenular collar (GFC) technique. J Pediatr Urol. 2017;13:34.e1-34.e6.
5. Saiad MO. The Modified Multilayer Coverage of Urethroplasty for Distal Hypospadias. J Indian Assoc Pediatr Surg. 2018;23:140-3.
6. Jesus LE, Schanaider A, Patterson G, Marchenko A, Aitken KJ, Leslie B, et al. Urethral compliance in hypospadias operated by tubularized incised urethral plate (TIP) with and without a dorsal inlay graft: an experimental controlled study. World J Urol. 2013;31:971-5.
7. Kurzrock EA, Jegatheesan P, Cunha GR, Baskin LS. Urethral development in the fetal rabbit and induction of hypospadias: a model for human development. J Urol. 2000;164:1786-92.
8. Leslie B, Jesus LE, El-Hout Y, Moore K, Farhat WA, Bägli DJ, et al. Comparative histological and functional controlled analysis of tubularized incised plate urethroplasty with and without dorsal inlay graft: a preliminary experimental study in rabbits. J Urol. 2011;186(4 Suppl):1631-7.
9. Singal AK, Dubey M, Jain V. Transverse preputial onlay island flap urethroplasty for single-stage correction of proximal hypospadias. World J Urol. 2016;34:1019-24.
10. Zhang S, Zhou C, Li F, Li S, Zhou Y, Li Q. Scrotal-Septal Fasciocutaneous Flap Used as a Multifunctional Coverage for Prior Failed Hypospadias Repair. Urol Int. 2016;96:255-9.
11. Tam YH, Pang KK, Wong YS, Tsui SY, Wong HY, Mou JW, et al. Improved outcomes after technical modifications in tubularized incised plate urethroplasty for mid-shaft and proximal hypospadias. Pediatr Surg Int. 2016;32:1087-92.
12. Pescheloche P, Parmentier B, Hor T, Chamond O, Chabaud M, Irtan S, et al. Tunica vaginalis flap for urethrocutaneous fistula repair after proximal and mid-shaft hypospadias surgery: A 12-year experience. J Pediatr Urol. 2018;14:421.e1-421.e6.
13. Beaudoin S, Delaage PH, Bargy F. Anatomical basis of surgical repair of hypospadias by spongioplasty. Surg Radiol Anat. 2000;22:139-41.
14. Yerkes EB, Adams MC, Miller DA, Pope JC 4th, Rink RC, Brock JW 3rd. Y-to-I wrap: use of the distal spongiosum for hypospadias repair. J Urol. 2000;163:1536-8.
15. Singal AK, Dubey M, Jain V. Transverse preputial onlay island flap urethroplasty for single-stage correction of proximal hypospadias. World J Urol. 2016;34:1019-24.
16. Acimi S. Anatomical Explanations of the Pathogenesis of Proximal Hypospadias. J Indian Assoc Pediatr Surg. 2019;24:97-9.
17. Almodhen F, Alzahrani A, Jednak R, Capolicchio JP, El Sherbiny MT. Nonstented tubularized incised plate urethroplasty with Y-to-I spongioplasty in non-toilet trained children. Can Urol Assoc J. 2008;2:110-4.

18. Hueber PA, Salgado Diaz M, Chaussy Y, Franc-Guimond J, Barrieras D, Houle AM. Long-term functional outcomes after penoscrotal hypospadias repair: A retrospective comparative study of proximal TIP, Onlay, and Duckett. J Pediatr Urol. 2016;12:198.e1-6.
19. Prakash G, Singh BP, Sinha RJ, Jhanwar A, Sankhwar S. Is circumferential urethral mobilisation an overdo? A prospective outcome analysis of dorsal onlay and dorso - lateral onlay BMGU for anterior urethral strictures. Int Braz J Urol. 2018;44:323-9.
20. Hafez AT, Herz D, Bägli D, Smith CR, McLorie G, Khoury AE. Healing of unstented tubularized incised plate urethroplasty: an experimental study in a rabbit model. BJU Int. 2003;91:84-8.

Correspondence address:
Senkai Li, MD
Hypospadias Treatment Center,
Plastic Surgery Hospital,
Peking Union Medical College
33 Ba-Da-Chu Rd, Shi Jing Shan District,
Beijing 100144, P. R. China
Fax: +86 106 886-4137
E-mail: dr_lsk@163.com

EDITORIAL COMMENT

Vol. 46 (3): 444-445, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0453.1

Editorial Comment: Effects of spongioplasty on neourethral function following hypospadias repair: an experimental study on rabbits

Antonio Macedo Jr. [1,2]

[1] Departamento de Urologia, CACAU-NUPEP, São Paulo, SP, Brasil; [2] Departamento de Pediatria, Universidade Federal de São Paulo, São Paulo, SP, Brasil

COMMENT

Authors have evaluated on an experimental study on rabbits the role of spongioplasty after urethral plate tubularization (Duplay technique) by assessing intraluminal urethral plate pressure and flow rate (ex vivo) (1). Two similar groups were created with exception for spongioplasty added to Duplay urethroplasty. Both groups presented similar results with no statistical differences. The fistula rate was higher in the no spongioplasty group (14.29%).

Barrier layers prevent fistula occurrence as shown here, but this is a well known concept that does not require further experimentation. The authors hypothesized that spongioplasty would compress or impact on urethra distensibility or compliance, which is not related to spongioplasty itself but to the degree of tension when suturing both wings of spongious tissue. This is a singularity of the procedure that can not be randomized and compared, because it is a surgical maneuver based on personal experience.

The authors are to be congratulated for the methodology of their work but in a translational world the surgeon awaits experimental studies to advance on relevant questions after clinical procedure. In hypospadias repair, the interposition of well vascularized tissue is desired and one can not omit using viable spongious tissue that has the advantage of being situated adjacent to the neourethra.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Xie L, Xi Y, Zhang X, Ding H, Li S. Effects of spongioplasty on neourethral function following hypospadias repair: an experimental study in rabbits. Int Braz J Urol. 2020;46: 436-43.

Antonio Macedo Jr.

Departamento de Pediatria
Universidade Federal de São Paulo - UNIFESP
Rua Maestro Cardim, 560 cj 215
São Paulo, SP, 01323-000, Brasil
E-mail: amcdjr@uol.com.br

ARTICLE INFO

Antonio Macedo Jr.
https://orcid.org/0000-0003-2545-5127

Int Braz J Urol. 2020; 46: 444-5

Submitted for publication:
December 16, 2019

Accepted after revision:
January 07, 2020

Published as Ahead of Print:
January 21, 2020

SURGICAL TECHNIQUE

Vol. 46 (3): 446-455, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0417

Modified wallace anastomotic technique reduces ureteroenteric stricture rates after ileal conduit urinary diversion

Petar Kavaric [1], Sabovic Eldin [1], Radovic Nenad [1], Pratljacic Dragan [1], Marko Vukovic [1]

1 Department of Urology, Clinical Center of Montenegro, Ljubljanska, Podgorica, Montenegro

ABSTRACT

Purpose: To compare perioperative outcomes, complications and anastomotic stricture rate in a contemporary series of patients who underwent open radical cystectomy (RC) with modified Wallace anastomotic technique versus traditional ileal conduit.
Materials and methods: Study enrolled 180 patients, of whom 140 were randomized and underwent RC; seventy were randomized to group I and the seventy to the group II. For the primary objective, we hypothesized that the rate of ureteroenteric strictures would be at least 20 % lower in the second group. Secondary end points included rate of anastomotic leak, surgical time, deterioration of the upper tract, intraoperative blood loss and patient-reported quality of life (HRQOL). The modified Wallace 1 technique involved eversion of the ureteral plate and bowel mucosa edges, which were anastomosed together in running fashion, while the outher anastomotic wall was augmented with sero-serosal interrupted sutures.
Results: The mean (SD) follow-up time was 26.1 (5.7) months in group I and 25.2 (4.8) months in group II, during which, anastomotic stricture was observed in 8 patients (12%) from the first and 2 patients (3%) from the second group ($p < 0.05$). The anastomotic leakage rate was significantly higher in first group (17% vs. 8.5%, $p< 0.05$), while patient-reported HRQOL outcomes were similar between groups after the 12 month follow-up period.
Conclusions: By using a modified Wallace technique, we were able to significantly lower anastomotic stricture and anastomotic leakage rates, which are major issues in minimizing both short- and long-term postoperative complications.

ARTICLE INFO

Marko Vukovic
http://orcid.org/0000-0003-0265-4721

Keywords:
Cystectomy; Urinary Diversion; Quality of Life

Int Braz J Urol. 2020; 46: 446-55

Submitted for publication:
June 24, 2019

Accepted after revision:
September 15, 2019

Published as Ahead of Print:
November 30, 2019

INTRODUCTION

Radical cystectomy (RC) is the standard management of non-metastatic invasive bladder cancer (BCa), and is curative in the majority of patients with localized disease. Despite the popularity of continent urinary diversion and neobladder reconstruction, radical cystectomy with ileal conduit urinary diversion remains the most common curative surgical approach for patients with invasive bladder cancer (1). In regard to anastomotic technique, two Wallace surgical techniques have been described: medial wall (Wallace 1) or head-to-tail (Wallace 2) anastomosis. However, both techniques are associated with risk of stricture (bilateral ureteral obstruction) at the site of

anastomosis (2). Ureteroileal anastomotic stricture (UAS) is an infrequent but potentially severe complication that may ultimately lead to renal impairment. In addition to patient- and disease-related risk factors, UAS can be a consequence of a poor surgical technique (3). Therefore, new techniques of ureteroileal anastomosis should be developed to reduce postoperative morbidity. For the primary end point, we hypothesized that the rate of ureteroenteric strictures would be at least 20% lower in the second group. Secondary end points included rate of anastomotic leak, surgical time, deterioration of the upper tract, intraoperative blood loss, rates of positive surgical margins (PSM), and patient-reported HRQOL outcomes 12-months post-operative. The objective of this study was to describe a modified Wallace I anastomosis surgical technique, and to compare perioperative outcomes, complications and anastomotic stricture rate in a contemporary series of patients who underwent open RC with modified Wallace anastomotic technique versus traditional ileal conduit.

MATERIAL AND METHODS

The surgical protocol was approved by the University of Montenegro institutional review board and registered with the Ethical comitee of Clinical centre of Montenegro (Nr. 03/01-517-1) and conducted in accordance with the principles of the Declaration of Helsinki of World Medical Association. All patients provided written consent prior to enrollment in surgery. Post-operative patients were followed for a minimum of 12 months to provide complications and health related quality of life (HRQOL) data. The European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Core Questionnaire version 3 was used to measure HRQOL (4-6). Questionnaires were self-administered by the patients and completed before surgery and at the 12-month follow-up visit.

BCa patients scheduled for definitive treatment by open RC plus pelvic lymph node dissection (PLND) and ileal conduit urinary diversion were recruited from the urology clinic at Clinical Centre of Montenegro between January 2010 and January 2016. Eligible patients were aged ≥30 years and had BCa clinical stage T2-T3/N0-3/M0. Patients were excluded if they had previous pelvic radiation, clinical stage T4 or M1, or extensive prior abdominal surgery. Patients who were lost or died during follow-up were excluded from the final analysis. Postoperatively, all patients were placed on the identical treatment pathway and were followed every 3-6 months with routine history and physical exams, diagnostic imaging of the chest/abdomen/pelvis, urine cytology, and complete blood work (7).

Patients were randomized to be treated with one of two surgical techniques. Group I consisted of 70 patients treated with the Wallace 1 technique, where ureteral medial walls were anastomosed together and the free edges of the newly constructed ureteral plate were anastomosed to the proximal end of an open bowel segment (ileum). Group II consisted of 70 patients treated with a modified Wallace 1 technique. The modified Wallace 1 technique involved eversion of the ureteral plate and bowel mucosa edges, which were anastomosed together in a running fashion, while the outer anastomotic wall was augmented with sero-serosal interrupted sutures and finally retroperitonealized. In both groups, men underwent removal of the prostate and women underwent hysterectomy and bilateral salpingo-oophorectomy, if these organs were present. The extent of the PLND was left to the discretion of the surgeon, based on clinician preference and judgment and at a minimum, hypogastric, obturator and external iliac lymph nodes were removed bilaterally (7). In the second group, lymph node dissection templates were standardised including obturator, external/internal/common iliac, and presacral nodes (8). Finally, in case of positive lymph nodes, extended dissections removed the lymph nodes overlying the aortic bifurcation and continued to the take-off of the inferior mesenteric artery.

SURGICAL TECHNIQUE

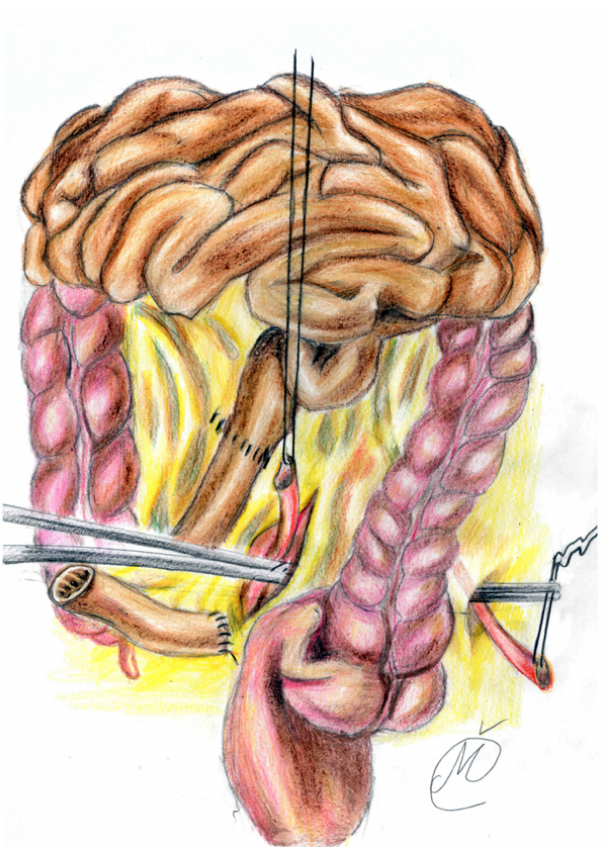
All surgical procedures were performed by a single expert, high-volume surgeon (P.K), who had a decade of experience in RC with Wallace 1 ileal conduit before the start of the study. After

completing RC, extended pelvic lymph node dissection was performed. After identification of the ileocecal valve and distal ileum, a 10-15cm long ileal segment was isolated, approximately 20cm proximal. A long and straight incision of the mesentery, on both ends, was made using the Harmonic Focus long shears (Ethicon Endo-Surgery Inc. Cincinnati, OH, USA). A side-to-side ileo-ileal anastomosis was performed using a PDS 4-0 continuous suture. The mesentery window was closed with interrupted sutures and the isolated segment was flushed with saline and povidone iodine. Next, ureters were conjoined, with the left ureter transposed to the right side of the pelvis through a tunnel prepared at the base of the sigmoid mesentery in front of the common iliac vessels (9) (Figure-1). The redundant tract of both ureters was resected in order to obtain a tension-free ureteroileal anastomosis without angulation (3) and to improve vascular supply of the distal ureteral plate. Both ureters were spatulated for 2cm and laid adjacent to each other; the apex of one ureter was sutured to the apex of the other ureter with 4-0 Vicryl or polydioxanone (PDS) sutures (10).

In group I, the posterior medial walls of spatulated ureters were sutured together with continuous 4-0 Vicryl suture (the knots tied to the outside), over a 6 ch ureteric catheter, while the lateral edges of the newly conjoined ureters were anastomosed to the proximal end of an open ileal conduit segment, using 4-0 PDS interrupted suture, according to the standard Wallace I technique (1, 11) (Figure-2).

In group II, the isolated ileal segment was 20cm long, while each ureter was spatulated for 2.5-3cm and initial 5-0 PDS suture was placed at the apex of both ureters through all layers. Next, the needle reverses posteriorly to facilitates further muco-mucosal running suture of everted posterior medial ureteral wall edges (4-0 Vicryl), over a 6 ch or 8 ch ureteric catheter (Figures 3 and 4). Lateral edges of the newly formed ureteral plate and the everted ileal mucosa (from the proximal end of conduit segment) were anastomosed in a running fashion (Figure-5), while the outher anastomotic wall was augmented with sero-serosal interrupted suture (Vicryl 4-0 or PDS 4-0). At the end, conduit was retroperitonealized with the ureterointestinal anastomosis being placed in the retroperitoneum (Figure-6). This was accomplished by suturing the serosa of the conduit to the posterior peritoneum, above the anastomosis. Finally, in both groups, an abdominal stoma in the right iliac fossa was performed. The distal end of the ileal segment was first anchored to the rectus fascia with interrupted 4-0 Vicryl sutures and then to the skin, while an 18 Ch Folley catheter was placed in the conduit to allow for postoperative flushing (3). A Jackson Pratt drain was placed in the retroperitoneum a few cm away from the anastomosis. Ureteric catheters were sequentially removed at 7 and 8 days if the ileus resolved, while the Jackson-Pratt drain was removed one day later, after checking the drain creatinine level (12). Following local protocol, loopogram studies were performed at 3, 6, and

Figure 1 - The mesentery window was closed with interrupted sutures, next, ureters were conjoined, with the left ureter transposed to the right side of the pelvis through a tunnel prepared at the base of the sigmoid mesentery in front of the common iliac vessels.



12 months, and then yearly, to assess for ureteroenteric anastomotic strictures (8).

Power calculations and statistical analysis

Statistical analysis was performed with SPPS v16.0 (SPPS, Chicago, IL, USA). Blood loss, operative time, and time to discharge (hospital stay) were assessed as continuous variables and tested for normalcy using the Kolmogorov test. The Student T test and Mann Whitney U test were used to determine statistical significance. Dichotomous variables were compared using the Fisher's exact tests. Spearman correlation analysis was used to determine the correlation between age and

Figure 2 - Ureters were spatulated and sutured together with continuous 4-0 Vicryl suture, while the lateral edges of the newly conjoined ureters were anastomosed to the proximal end of an open ileal conduit segment, using 4-0 PDS interrupted suture, according to the standard Wallace I technique.

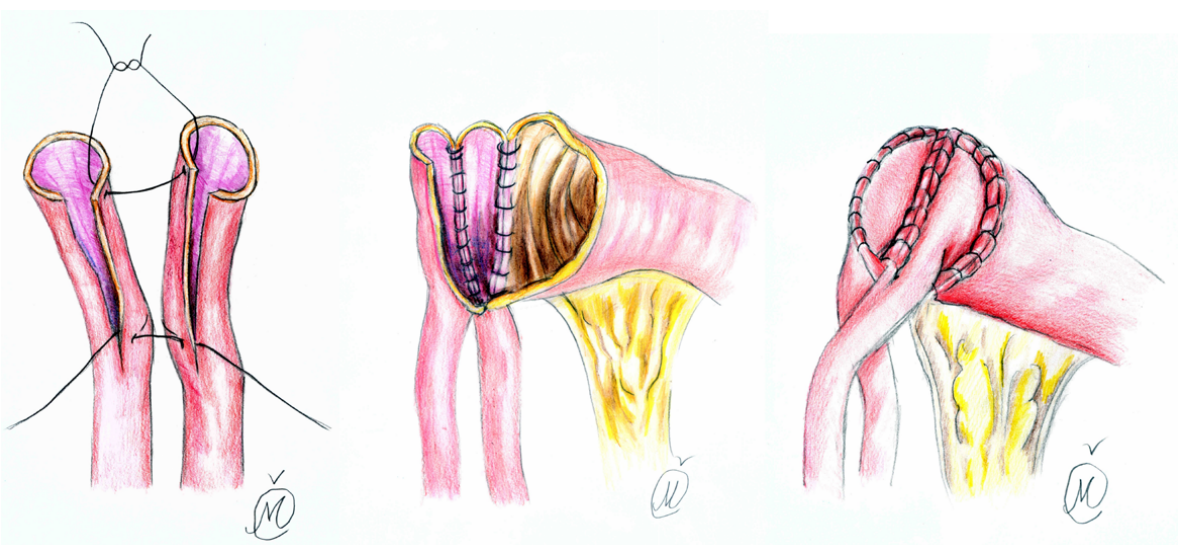


Figure 3 - After each ureter spatulation, initial 5-0 PDS suture was placed at the apex of both ureters through all layers with muco-mucosal running suture of everted posterior medial ureteral wall edges (4-0 Vicryl), over a 6 ch or 8 ch ureteric catheter.

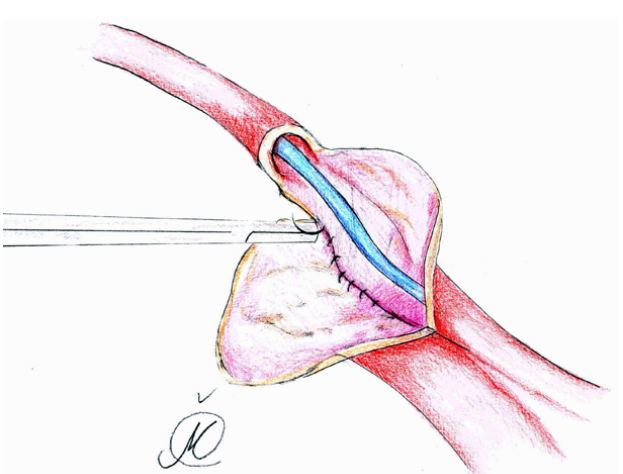


Figure 4 - The needle reverses posteriorly to facilitates further muco-mucosal running suture of postero-medial ureteral wall edges (4-0 Vicryl), while several anterior wall sutures complete ureteral plate anastomosis.

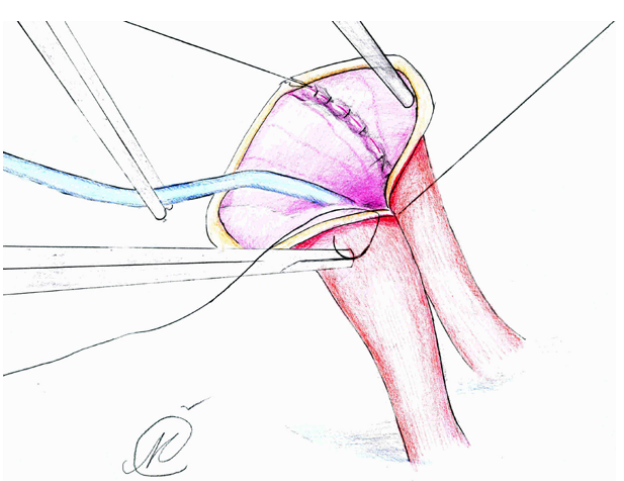


Figure 5 - Lateral edges of the newly formed ureteral plate and the everted ileal mucosa (from the proximal end of conduit segment) were anastomosed in a running fashion.

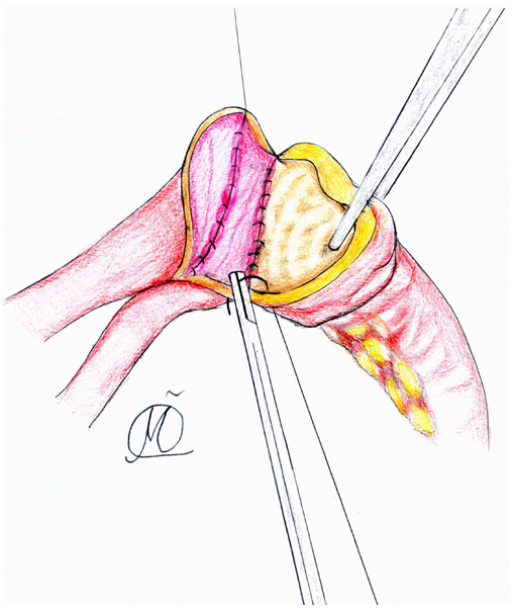
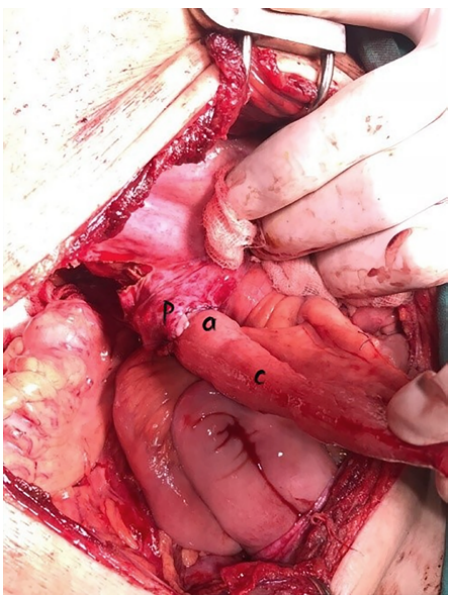


Figure 6 - Ureteroenteric anastomosis with retroperitoneal-isation of anastomotic line: a) peritoneal flap; b) ureteroenteric anastomotic site; c) conduit segment.



baseline QoL scores. The difference between obtained values was considered significant when p <0.05, and highly significant when p <0.01. We also present descriptive statistics such as mean (SD) values, percentages and interquartile range (IQR), generated with SPSS.

RESULTS

Our study enrolled 180 patients, of whom 140 were randomized and underwent RC/PLND; seventy were randomized to group I and seventy to the group II. Post-randomization distributions of group demographics, disease characteristics, and pathologic staging were not significantly different (Table-1). The mean (SD) follow-up time was 26.1 (5.7) months in group I and 25.2 (4.8) months in group II. Overall, there were 12 patients who experienced local recurrences (8.5%), and a total of 6 deaths were observed, 3 of which from BCa. These were excluded from the study. Neoadjuvant chemotherapy was given to 26 (37.14%) patients treated with standard technique and to 23 (32.8%) patients treated with the modified Wallace technique. PLND was performed in 60 patients (85.7%) in group I and in 63 patients (90%) in the group II (Table-1). There was no difference in the lymph node yield based on the extent of dissection between groups (4.3% vs. 4.9%). Mean blood loss was 810±250mL and 780±320mL in first and second groups, respectively.

During the follow-up period, anastomotic stricture was observed in 8 patients (12%) from the first and 2 patients (3%) from the second group (95% confidence interval for difference, p <0.05) (Table-1). The anastomotic stricture was diagnosed after new onset of hydrouretero-nephrosis (HUN) or after an increase in the preexisting HUN was visualized by CT scan and confirmed by loopogram (13). Four patients from group I and one patient from group II underwent antegrade DJ stent placement, one patient from group I and the patient from group II received percutaneous nephrostomy tube (PCN) as a definitive treatment. The remaining 3 patients (all in group I) underwent uretero-intestinal reimplantation. None of the patients with UAS were managed conservatively. Additionally, two patients from the group I (2.8%) developed left ureteral stenosis, proximal to the anastomotic site, both were managed conservatively. No patients from group II developed left ureteral stenosis. Surgical margin positiv-

Table 1 - Patient characteristics and comparison of perioperative outcomes between groups.

Mean (SD)/Percentage (%)		
Demographic & pathological characteristics	Wallace I; (n=70)	Modified Wallace I; (n=70)
Age (years)	64 (17.26)	61 (14.12)
BMI, kg/m², mean (SD)	22.5 (3.2)	23.8 (2.6)
Follow-up time, mean (SD)	26.1 (5.7)	25.2 (4.8)
Male, n (%)	34 (48.5)	38 (54.2)
Female, n (%)	36 (51.5)	32 (45.8)
ASA score, n (%)		
2	21 (30)	24 (34.2)
≥3	49 (70)	46 (65.8)
Pathologic stage, n (%)		
T2	25 (35.7)	31 (44.28)
T3	45 (64.3)	39 (55.72)
Lymph node-positive patients, n (%)	43 (61.4)*	30 (42.8)
Operative time (min.), SD	260 (25.31)*	330 (32.1)
Estimated blood loss (mL), SD	810 (250)	780 (320)
Hospital stay (days), SD	21 (4.6)	19 (3.4)
Transfusion rate, n (%)	10 (14.2)	12 (17.1)
Postoperative complications, n (%)		
Paralitic ileus	11 (13.8)	17 (20.2)
Renal insufficiency	5 (7.14)	2 (3)
Pneumonia	11 (15.7)*	21 (30)
Pyelonephritis	27 (38.5)	12 (17.1)*
Anastomotic leakage rate, n (%)	12 (17)	6 (8.5)*
Anastomotic stricture rate, n (%)	8 (12)	2 (3)*
Stricture treatment, n (%)	8 (100)	2 (100)*
Antegrade DJ stent placement	4 (77.5)	1 (50)
Percutaneus nephrostomy (PCN)	1 (10)	1 (50)
Uretero-Intestinal reimplantation (UIR)	3 (12.5)	0*
Relapse on follow-up, n (%)	7 (10)	5 (7.1)

*statistically significant difference between two groups ($p < 0.05$)

ity did not differ significantly between groups (5.7% vs. 4.2%). The anastomotic leakage rate was significantly higher in first group (17% vs. 8.5%, p=0.03), as well as lymph node positivity (61.4% vs. 42.8%, p=0.04). Paralitic ileus was the most common early complication in both groups (14% vs. 20%), followed by pyelonephritis and pneumonia (Table-1). Patient-reported HRQOL outcomes were similar between groups after the 12 month follow-up period (Table-2).

During the follow-up period, mild metabolic acidosis was observed in 3 patients (4.2%) from the first and 6 patients (8.5%) from the second group and effectively treated with alkalinizing agents. The presence of more than a mild acidosis, which prompt an evaluation for obstruction or redundancy of the conduit, was not observed in second group, despite longer ileal segment.

DISCUSSION

UAS is a well-documented complication after RC which can result in irreversible damage to the corresponding renal unit; the associated surgical revision also carries additional risk of morbidity (3). The long-term incidence of UAS after ileal conduit diversion ranges widely, between 2-22% (14-17). While the exact mechanisms of benign stricture formation are not known, it is thought to be predominantly due to ischaemia and subsequent scarring at the anastomosis (18). Although poor surgical technique and extensive ureteral mobilization could be major risk factors for UAS, it is

Table 2 - EORTC QLQ-C30 scores preoperatively and at 12 months follow-up in the Wallace group (n=70) and the modified Wallace group (n=70).

Mean (SD) EORTC QLQ - C30 score (modified)				
	Preoperatively		12 - month follow-up	
	Group I	Group II	Group I	Group II
	(Wallace)	(Modified Wallace)	(Wallace)	(Modified Wallace)
Function scale				
Physical	71.3 (13.7)	73.5 (14.3)	74.6 (11.7)	77.9 (12.1)
Cognitive	69.1 (20.6)	81.5 (15.8)*	72.1 (14.6)	75.7 (13.8)
Emotional	68.3 (14.6)	72.7 (13.5)	56.3 (14.6)	68.2 (14.5)*
Social	71.3 (9.7)	77.6 (12.8)	60.5 (10.5)	75 (13.8)*
Global health status -QoL	46.3 (12.6)	50.2 (18.5)	48.7 (13.9)	52.6 (16.5)
Symptom scale				
Dyspnea	15.3 (12.7)	12.6 (11.3)	17.3 (10.7)	15.8 (11.2)
Pain	31.3 (14.2)	33.1 (12.7)	24.3 (15.2)	23.4 (11.7)
Nausea/Vomiting	9.5 (5.4)	7.3 (6.6)	9.1 (10.2)	7.7 (8.6)
Constipation	18.9 (17.7)	21.7 (13.4)	19.2 (18.7)	15.6 (11.4)
Diarrhoea	9.8 (4.1)	12.5 (7.2)	13.7 (9.3)	10.1 (7.3)
Financial difficulty scale	57.9 (29.5)	39.2 (35)*	66.2 (24.3)	60.2 (21)

*statistically significant difference between two groups ($p < 0.05$)

evident that other factors may jeopardize the blood supply to the distal tract of the ureter, increasing the risk of stricture (3). Short ureteral spatulation, high tension on ureteroileal anastomosis, or short conduit segment are well known factors. Nevertheless, the type of anastomotic suture on ureteral plate and ureteroileal anastomosis may play significant roles in reducing UAS rate. According to our results, muco-mucosal running suture of conduit anastomosis augmented with interrupted sero-serosal suture, paired with longer ileal segment and longer ureteral spatulation, leads to a significantly lower rate of uretero-ileal stricture as compared to the standard Wallace I technique (3% vs. 12%, p=0.02). These findings bolster the assertion that meticulous handling, preparation and fine suturing technique of distal ureter are essential to minimize the risk of postoperative strictures and urinary leak (19). Indeed, our study also found a significantly lower rate of anastomotic leak among patients treated with modified Wallace I technique (8.5% vs. 17%, p=0.04). A study carried out by Katherine AA et al. (20) showed that the associated factors with increased risk of benign UAS include higher body mass index (BMI), ASA score >2, lymph node involvement, male sex, and a history of previous abdominal surgery. In our study, 100% of patients with UAS showed evidence of lymph node involvement and anastomotic leak, while ASA score >2 was determined in 80% of patients, suggesting that these variables may have predictive value on UAS.

Although anastomotic leak is one of the most challenging adverse events, occurring in up to 7% of cases (21), this complication could be prevented with adequate surgical technique, such as low tension at the anastomosis, long ureteral spatulation, and proper suturing technique (14). Muco-mucosal anastomotic pattern could reduce the anastomotic tension and occurrence of ureteral devascularization. Additionally, sero-serosal interrupted suture may improve the watertight of anastomotic line. All these factors, together with longer ureteral spatulation, proper length of ileal segment, ureteric catheter placement and excision of redundant ureteral tracts, could significantly lower the incidence rate of UAS and anastomotic leak.

Nevertheless, the rate of anastomotic leak is still high in our series compared to rates reported in current literature (14, 15, 22), indicating that meticulous surgical technique needs to be improved. However, this remains controversial (10), as early studies showed that everting anastomosis significantly increases the chances for severe adhesions (23). The findings we report support the opposite conclusion. In addition, Chen et al. (24) claim that continuous suture has no advantage over interrupted in bowel anastomosis, and neither does two layer (as compared to single layer) anastomosis. Other groups have reported that sero-serosal interrupted suture between ureter and ileum avoids the incidence of stenosis and preserves the upper tract (25), our findings align with that conclusion. Despite attention to surgical technique, devascularisation can still occur. Introduction of Intravenous Indocyanine green (ICG) may facilitate assessment of distal ureteric vascularity in patients undergoing uretero-enteric anastomosis and may reduce the risk of uretero-enteric anastomotic stricture following surgery (18).

According to contemporary literature (26), excluding UAS, the three most common complications associated with ileal conduit diversion are pyelonephritis (5-23%), urinary calculi (3-16%) and stomal complications. In our study, the incidence of postoperative complications varied between treatment groups. The most common postoperative complication was pyelonephritis (38% vs. 17.1%), followed by pneumonia (15.7% vs. 30%), paralitic ileus and anastomotic leak. The high incidence of pyelonephritis among patients treated with standard Wallace I technique is likely associated with the high rate of anastomotic leak (17%), which will certainly lead to renal impairment over time. While it is early to discuss renal deterioration two years post-operative, 7.5% of patients from the first group have already developed renal insufficiency. However, members of group II (who were treated with modified Wallace I technique) had a significantly lower incidence of pyelonephritis (17.1%) and a lower (though not significantly) occurrence of renal insufficiency (3%). This indicates the importance and effectiveness of our technique in reducing postoperative complication rates and precluding renal impair-

ment. However, a longer follow-up period would provide stronger evidence of the impact of our technique on the incidence of renal impairment after RC.

In the present study, the baseline characteristics of the patients and QoL were measured immediately and 12 months postoperatively. Our treatment groups were similar with regard to the majority of baseline characteristics, lymph node positivity being an important exception. It is commonly believed that there are differences in the QoL outcomes of various diversions, but there are no published studies that have conclusively documented the superiority of one technique in terms of QoL (27, 28). Our results, however, demonstrate that patient self-rated emotional and social functional were significantly lower postoperatively among those in group I (56.3 vs. 68.2, 60.5 vs. 75). On the other hand, patients from group II remained in the same functional range as before surgery. This result is associated with lower incidence of UAS, urinary leakage, and pyelonephritis. This is additionally associated with less invasive treatment required, with regard to stricture.

The limitations of this study are the small size of randomization groups and the short follow-up period. In addition, the unusually high rate of anastomotic leak in patients within the first group could lead to research bias regarding effectiveness of modified Wallace technique, although the postoperative leakage rate was significantly reduced compared to first group. Nevertheless, single surgeon experience could be the major reason for this bias, which could be addressed by involving other highly trained surgeons. Finally, our quality of life questionnaire is simplified and not bladder cancer-specific, therefore urinary diversion-specific problems (urostomy problems, sexual functioning, etc.) were not assessed. Had we been able to use a bladder cancer-specific instrument, we could have more easily identified the causes of differences in QoL scores between the groups (6).

CONCLUSIONS

By using a modified Wallace technique, we were able to significantly lower anastomotic stricture and anastomotic leakage rates, which are major issues in minimizing both short- and long-term postoperative complications. The present study provides important information about differences in QoL domains between patients undergoing standard Wallace I versus modified surgical technique, and the probable reasons behind these observed differences. Finally, additional studies with a longer follow-up period are necessary, as the endpoint of this study was too early to capture the majority of benign ureteroenteric strictures.

ACKNOWLEDGEMENTS

The authors would like to thank Ms Cavelis Mila for illustrations and technical support.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Davis NF, Burke JP, McDermott T, Flynn R, Manecksha RP, Thornhill JA. Bricker versus Wallace anastomosis: A meta-analysis of ureteroenteric stricture rates after ileal conduit urinary diversion. Can Urol Assoc J. 2015;9:E284-90.
2. Evangelidis A, Lee EK, Karellas ME, Thrasher JB, Holzbeierlein JM. Evaluation of ureterointestinal anastomosis: Wallace vs Bricker. J Urol. 2006;175:1755-8.
3. Ficarra V, Giannarini G, Crestani A, Palumbo V, Rossanese M, Valotto C, et al. Retrosigmoid Versus Traditional Ileal Conduit for Urinary Diversion After Radical Cystectomy. Eur Urol. 2019;75:294-9.
4. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365-76.
5. Singh V, Yadav R, Sinha RJ, Gupta DK. Prospective comparison of quality-of-life outcomes between ileal conduit urinary diversion and orthotopic neobladder reconstruction after radical cystectomy: a statistical model. BJU Int. 2014;113:726-32.
6. Fayers P, Bottomley A; EORTC Quality of Life Group; Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer. 2002;38(Suppl 4):S125-33.

7. Bochner BH, Dalbagni G, Marzouk KH, Sjoberg DD, Lee J, Donat SM, et al. Randomized Trial Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: Oncologic Outcomes. Eur Urol. 2018;74:465-71.
8. Khan MS, Gan C, Ahmed K, Ismail AF, Watkins J, Summers JA, et al. A Single-centre Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL). Eur Urol. 2016;69:613-21.
9. Colombo R, Naspro R: Ileal conduit as the standard for urinary diversion after radical cystectomy for bladder cancer. Eur Urol Suppl. 2010; 10:736-44.
10. Dahl DM: Use of Intestinal segments in Urinary diversion. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA. Campbell-Wallsh Urology. Philadelphia, Elsevier. 2016; pp. 2281-4.
11. Wallace DM. Ureteric diversion using a conduit: a simplified technique. Br J Urol. 1966;38:522-7.
12. Traver MA, Vaughan ED, Porter CR. Radical retropubic cystectomy. BJU Int. 2009;104:1800-21.
13. Baten E, Akand M, Floyd MS Jr, Van Cleynenbreugel B, Albersen M, Everaerts W, et al. Evaluation of conservative approach in the management of ureteroenteric strictures following radical cystectomy with Bricker ileal conduit: a single-center experience. Scand J Urol. 2016;50:439-44.
14. Madersbacher S, Schmidt J, Eberle JM, Thoeny HC, Burkhard F, Hochreiter W, et al. Long-term outcome of ileal conduit diversion. J Urol. 2003;169:985-90.
15. Lawrentschuk N, Colombo R, Hakenberg OW, Lerner SP, Månsson W, Sagalowsky A, et al. Prevention and management of complications following radical cystectomy for bladder cancer. Eur Urol. 2010;57:983-1001.
16. Madersbacher S, Möhrle K, Burkhard F, Studer UE. Long-term voiding pattern of patients with ileal orthotopic bladder substitutes. J Urol. 2002;167:2052-7.
17. Palascak P, Bouchareb M, Zachoval R, Urban M, Sauvain JL, Palascak R. Treatment of benign ureterointestinal anastomotic strictures with permanent ureteral Wallstent after Camey and Wallace urinary diversion: long-term follow-up. J Endourol. 2001;15:575-80.
18. Ahmadi N, Ashrafi AN, Hartman N, Shakir A, Cacciamani GE, Freitas D, et al. Use of indocyanine green to minimise uretero-enteric strictures after robotic radical cystectomy. BJU Int. 2019;124:302-7.
19. Nagele U, Sievert KD, Marseburger AS, Anastasiadis AG, Stenzl A: Urinary diversion following cystectomy. EAU Update Series. 2005; 3:129-37.
20. Katherine A A, Emily A V, Gillian S, Ali F, Daniel D S, S Machele D, et al. Predictors of Benign Uretero-enteric Anastomotic Strictures After Radical Cystectomy and Urinary Diversion. Urology. 2018. [Ahead of Print]
21. Farnham SB, Cookson MS. Surgical complications of urinary diversion. World J Urol. 2004;22:157-67.
22. Dahl MD: Complications: Ileal Conduit, In: Wein AJ, Kavoussi LR, Partin AW, Peters CA. Campbell-Wallsh Urology. Philadelphia, Elsevier. 2016; pp. 2306-7.
23. Mellish RW. Inverting or everting sutures for bowel anastomoses. An experimental study. J Pediatr Surg. 1966;1:260-5.
24. Chen C. The art of bowel anastomosis. Scand J Surg. 2012;101:238-40.
25. Wishahi MM, Elganzoury H, Elkhouly A, Mehena A. Dipping technique for ureteroileal anastomosis in orthotopic ileal neobladder: 20-year experience in 670 patients-no stenosis with preservation of the upper tract. ISRN Urol. 2013;2013:725286.
26. Lee RK, Abol-Enein H, Artibani W, Bochner B, Dalbagni G, Daneshmand S, et al. Urinary diversion after radical cystectomy for bladder cancer: options, patient selection, and outcomes. BJU Int. 2014;113:11-23.
27. Porter MP, Wei JT, Penson DF. Quality of life issues in bladder cancer patients following cystectomy and urinary diversion. Urol Clin North Am. 2005;32:207-16.
28. Somani BK, Gimlin D, Fayers P, N'dow J. Quality of life and body image for bladder cancer patients undergoing radical cystectomy and urinary diversion-a prospective cohort study with a systematic review of literature. Urology. 2009;74:1138-43.

Correspondence address:
Marko Vukovic, MD
Department of Urology, Clinical centre of Montenegro, Ljubljanska
81000 Podgorica, Montenegro
Telephone: + 382 69 498879
E-mail: marko.vukovic09@gmail.com

EXPERT OPINION

Vol. 46 (3): 456-458, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.02

Use of 5α-reductase inhibitor and delay in prostate cancer diagnosis and treatment

Wilson F. S. Busato Júnior [1, 2]

[1] Disciplina de Urologia, Universidade do Vale do Itajaí - Univali, Itajaí, SC, Brasil; [2] Departamento de Uro-Oncologia, Sociedade Brasileira de Urologia - SBU, Rio de Janeiro, RJ, Brasil

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) and its associated symptomatology affect many men worldwide, the prevalence is over 210 million men and up to 50% of men >50 year-old experience LUTS from BPH (1). BPH has been linked to two factors: age and the presence of testosterone and two drug classes became accepted standard of care 3 decades ago: 5-alpha-reductase inhibitors (5-ARI) and Alpha-blockers (2). The 5-ARI block the intra-prostatic conversion of testosterone to more potent androgen dihydrotestosterone (DHT) and thus reduce the growth effects of androgens on the prostate (3). But 5-ARI also depress serum prostate-specific antigen (PSA) concentrations by approximately 50% (4). In 2003 an article with 18,000 men who randomly were assigned to receive either 5 mg of finasteride or a placebo, the finasteride group had a 25% lower risk of being diagnosed with prostate cancer (PC), but a 68% higher risk of being diagnosed with a high-grade (HG) disease. That study encourage urologists and general practioners (GP) to prescribe finasteride for PC prevention (5). Recently, an article has reopened an important discussion: Can 5-ARI use delay PSA-based PC diagnosis or even increase the risk of a more advanced PC at time of diagnosis when PSA's effect is disregarded (6).

The 5-ARI acts by preventing the intracellular conversion of testosterone to DHT. However, this enzyme does not occur in normal or even malignant prostatic epithelial cells, but in stromal cells. Etzioni et al. demonstrated that significant PC (GS>6) rarely occur in prostatic stroma, thus 5-ARI would have little effect on **GS≥7** PC, not benefiting in the reduction of these cases (7). But 5-ARI has the ability to reduce PSA production by the prostatic stroma. So, men using 5-ARI need to have their PSA multiplied by factor 2 in the first 2 years of use, by 2.3 between 2 and 7 years and by 2.5 after 7 years of use. Using this correction, screening remains effective in men using 5-ARI (7).

The concern is that these drugs are widely used to treat BPH for long periods of time and are often prescribed by non-urologists. Approximately 90% of PSA screening tests are ordered in primary care by GPs or internists, just 7% were ordered by urologists (8, 9). There is no reliable data in Brazil and it is believed that between 25-30% of PSAs are requested by urologists in private health insurance. But in the public system, serving 70% of the population, the situation is quite different. The official recommendation is that "... upon initial evaluation by the GP, men with suspected PC should be referred to medium-complexity outpatient clinics where the urologist makes the diagnos-

tic investigation." (10). Finasteride is offered by the public system at no charge. Thus, the suppression of PSA by 5-ARI may not be taken into consideration, delaying the time to refer to the urologist, to biopsy indication and, consequently, worsening oncological results. Men diagnosed with local or regional metastasis from PC have a 5-year survival of 99%; however, men diagnosed with distant disease have a 29% chance of 5-year survival (11).

In the study 80,875 men from the Veterans Affairs Health Care System were evaluated where 8,587 were using 5-ARI at the time of diagnosis of PC. Comparing with those who did not use, these men had longer time between PSA elevation (3.6 years vs. 1.4 years) and biopsy. The mean adjusted PSA at the time of biopsy was significantly higher for 5-ARI users than non-users (13.5 ng/mL vs 6.4 ng/mL). Patients treated with 5-ARI were more likely to have GS≥8 (25.2% vs 17.0%), clinical stage ≥T3 (4.7% vs 2.9%), positive lymph nodes (3.0% vs 1.7%) and metastatic disease (6.7% vs 2.9%) than non-users. Finally, this study found 5-ARI users to be at greater risk for PC specific mortality than non-users (13% vs 8%), corresponding to an adjusted 39% incremental risk. They concluded that the pre-diagnosis use of 5-ARI was associated with a late diagnosis and worse cancer-specific outcomes in men with PC. Highlight the continuing need to raise awareness about 5-ARI-induced PSA suppression among non-urologists (6).

One of the possible reasons why GPs do not adjust PSA in men taking 5-ARI is the lack of information about it. In fact, the guidelines (AUA, ASCO, UAE, BSU) do not recommend a PSA cutoff in men using 5-ARI to indicate biopsy. It would be important for societies to campaign among all primary care physicians to clarify this issue. Another possible cause is the combined use of 5-ARI with alpha-blockers (combo) that may lead non-urologists to misperceive as monotherapy. On the other hand, urologists need to discuss these issues related to 5-ARI use with patients, explaining that PSA should continue to fall while taking medication and that if there is an increase, the risk of cancer increases by 3x and the risk of a high grade disease increases by 6x (12).

Finally, it is worth leaving Dr. Resnick's words: "... the available data suggest that 5-ARI use is safe. What is not safe, however, is ignoring the PSA suppression associated with 5-ARI therapy."nfer some protection to the urinary tract function.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Lokeshwar SD, Harper BT, Webb E, Jordan A, Dykes TA, Neal DE Jr, Terris MK, Klaassen Z. Epidemiology and treatment modalities for the management of benign prostatic hyperplasia. Transl Androl Urol. 2019;8:529-39.
2. Lepor H. Medical treatment of benign prostatic hyperplasia. Rev Urol. 2011;13:20-33.
3. Goldenberg L, So A, Fleshner N, Rendon R, Drachenberg D, Elhilali M. The role of 5-alpha reductase inhibitors in prostate pathophysiology: Is there an additional advantage to inhibition of type 1 isoenzyme? Can Urol Assoc J. 2009;3(3 Suppl 2):S109-14.
4. Rittmaster RS. 5alpha-reductase inhibitors in benign prostatic hyperplasia and prostate cancer risk reduction. Best Pract Res Clin Endocrinol Metab. 2008;22:389-402.
5. Goodman PJ, Tangen CM, Darke AK, Lucia MS, Ford LG, Minasian LM, et al. Long-Term Effects of Finasteride on Prostate Cancer Mortality. N Engl J Med. 2019 Jan 24;380:393-4.
6. Sarkar RR, Parsons JK, Bryant AK, Ryan ST, Kader AK, McKay RR, et al. Association of Treatment With 5α-Reductase Inhibitors With Time to Diagnosis and Mortality in Prostate Cancer. JAMA Intern Med. 2019;179:812-9.
7. Etzioni RD, Howlader N, Shaw PA, Ankerst DP, Penson DF, Goodman PJ, et al. Long-term effects of finasteride on prostate specific antigen levels: results from the prostate cancer prevention trial. J Urol. 2005;174:877-81.
8. Wahl PM, Timmerman J, Mammone V, Blunt AG, Anastassopoulos KP. Trends in prostate cancer screening before and after publication of US Preventive Services Task Force draft guidelines: an analysis of data from a large US Laboratory Service Provider. Value in Health 2016;19:A312-PMD85
9. Rosenberg M, Crawford D, Newmark J, Steiner M. Use of PSA screening guidelines among primary care physicians. J Urol 2016;195(4S. supplem):MP39-01.

10. [No Authors] DATASUS/SAI. Detecção Precoce – Informativo. Boletim ano 8, número 2, 2017: <http://www.saude.df.gov.br/wp-conteudo/uploads/2018/03/Informativo-Câncer-de-Próstata-2017.pdf> (accessed in December 17, 2019).
11. Thompson IM, Pauler Ankerst D, Chi C, Goodman PJ, Tangen CM, Lippman SM, et al. Prediction of prostate cancer for patients receiving finasteride: results from the Prostate Cancer Prevention Trial. J Clin Oncol. 2007;25:3076-81.
12. Liss MA, Thompson IM. Prostate cancer prevention with 5-alpha reductase inhibitors: concepts and controversies. Curr Opin Urol. 2018;28:42-5.

Wilson F. S. Busato Júnior, MD

Disciplina de Urologia
Universidade do Vale do Itajai - UNIVALI
Av. Marcos Konder, 1203
Itajai, SC, 88301-303, Brasil
E-mail: wbusato@gmail.com

ARTICLE INFO

Wilson F. S. Busato Jr.
https://orcid.org/0000-0001-7960-9609

Int Braz J Urol. 2020; 46: 456-8

Submitted for publication:
January 06, 2020

Accepted:
February 04, 2020

UPDATE IN UROLOGY

RENAL PELVIS AND URETER CANCER

Vol. 46 (3): 459-460, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.03

Editorial Comment: Diagnostic ureteroscopy prior to nephroureterectomy for urothelial carcinoma is associated with a high risk of bladder recurrence despite technical precautions to avoid tumor spillage

Baboudjian M [1], Al-Balushi K [1], Michel F [1], Lannes F [2], Akiki A [1], Gaillet S [1,2], Delaporte V [2], Ragni E [2], Toledano H [2], Karsenty G [1], Rossi D [2], Bastide C [2], Lechevallier E [1], Boissier R [3]

[1] Department of Urology and Renal Transplantation, La Conception University Hospital, APHM, Aix-Marseille University, 13005, Marseille, France; [2] Department of Urology, Nord University Hospital, APHM, Aix-Marseille University, Marseille, France; [3] Department of Urology and Renal Transplantation, La Conception University Hospital, APHM, Aix-Marseille University, 13005, Marseille, France

World J Urol. 2020 Jan;38(1):159-165

DOI: 10.1007/s00345-019-02768-w | **ACCESS:** 10.1007/s00345-019-02768-w

João Paulo Martins de Carvalho [1]

[1] Serviço de Urologia, Hospital Federal Cardoso Fontes, Rio de Janeiro, RJ, Brasil

COMMENT

The use of flexible ureterorenoscopy for the diagnosis (DFU) of suspected lesions in the renal pelvis, calyx and other segments of the collecting system is common in urology. This elegant work tries to use a systematization of the surgical access in order to evaluate the possibility of tumor spillage in other urinary segments, when handling is diagnostic or therapeutic in urothelial tumors.

This is a single center study where patients underwent DFU prior to the procedure of radical nephro ureterectomy (RNU) from 2005 to 2017.

The great merit of this work was the definition of the following DFU operative technique:

1. A ureteropyelography with a ureteral catheter 7Fr with diluted contrast. Placement of a guide wire under visual and fluoroscopic control;
2. Placement of Ch 9-10 Peel-Away ureteral sheath on the guide wire. In case of UTUC in the ureter, the Peel- Away was placed just below the tumor and was then peeled to the urethral meatus;
3. A flexible ureteroscope was inserted in the ureteral sheath and selective cytology was performed close to the larger tumor;
4. A biopsy of the larger tumor was performed with a forceps biopsy
5. Complete exploration of the renal cavities was performed. Irrigation was provided with saline serum and a pressurized pump.

6. Retrograde ureteroscopy was performed and the ureteral sheath was removed with the ureteroscope. Drainage consisted of a mono-J + bladder catheter which was both removed on D1-D2 if no fever or significant bleeding was occurring.

Mostly important, no patient received postoperative endovesical instillation (EVI) after DFU.

RNU was performed after DFU, by open or laparoscopic access according to the surgeon's preference and bladder cuff excision without the endoscopic approach. Postoperative EVI began in March 2016.

All patients had preoperative endoscopic and tomographic staging to rule out metastases or multicenter tumors. Postoperative follow-up was performed according to the institution's protocol.

At the end, the patients were stratified into two groups before the RNU: those who underwent DFU (DFU+) and those who did not (DFU-). In a total of 171 patients who underwent RNU, 93 were included in the protocol: 70 - DFU+ and 23 - DFU -.

There was no statistical difference when comparing the baseline criteria between the two groups: age, tumor stage and tumor grade, postoperative pain analysis or positive surgical margins.

At the 35-month postoperative follow-up, DFU+ patients had a bladder recurrence (BR) up to 87%. No risk factor for BR other than DFU was found in a multivariate statistical analysis.

Despite the technical care, the odds ratio for DFU+ was 4.0. However, as reported by the authors, BR presented neoplasms of less aggressive behavior, low risk and superficial diseases, even if multifocal. There was no long-term impairment in overall survival, cancer-specific survival, and metastasis-free survival.

The reference cited by the authors places as risk factors for BR the presence of previous bladder neoplasia, high-grade neoplasms, urinary cytology prior to the RNU (1). Even so, this multivariate analysis did not use DFU as a risk factor for BR. Thus, the authors interpreted that factors linked to primary neoplasia could be more determinant than DFU itself for the presence of BR.

As reported, many studies cite DFU but without elucidating its technique, presence of ureteric sheaths, or confirmatory biopsy. Most importantly, in this study, all patients who had a history of previous resection of bladder neoplasms were excluded.

The authors also mention that despite RNU in high-grade urothelial tumors, intra-bladder recurrence was of low-grade neoplasms. This supports the need for further studies to decrease BR after DFU, such as intra-vesical chemotherapy, which is already performed after RNU.

REFERENCES

1. Seisen T, Granger B, Colin P, Léon P, Utard G, Renard-Penna R, et al. A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol. 2015;67:1122-33.

João Paulo Martins de Carvalho, MD

Serviço de Urologia, Hospital Federal Cardoso Fontes, Rio de Janeiro, RJ, Brasil
E-mail: carvalho.jpm@gmail.com

ARTICLE INFO

João Paulo Martins de Carvalho
https://orcid.org/0000-0001-9534-2393

Int Braz J Urol. 2020; 46: 459-60

UPDATE IN UROLOGY

MALE HEALTH

Vol. 46 (3): 461-462, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.04

Editorial Comment: Penile prosthesis implant in the special populations: diabetics, neurogenic conditions, fibrotic cases, concurrent urinary continence surgery, and salvage implants

Chung E [1, 2, 3]

[1] *AndroUrology Centre, Brisbane, QLD 4000, Australia; 2 University of Queensland, Princess Alexandra Hospital, Brisbane, QLD 4000, Australia; 3 Macquarie University Hospital, Sydney, NSW 2109, Australia*

Asian J Androl. 2020 Jan-Feb;22(1):39-44

DOI: 10.4103/aja.aja_127_19 | **ACCESS:** 10.4103/aja.aja_127_19

Valter Javaroni [1]

[1] *Departamento de Andrologia, Hospital Federal do Andaraí Rio de Janeiro, Rio de Janeiro, RJ, Brasil*

COMMENT

In this invited review Dr. Chung from Australia presented a good revision on Penile Prosthesis Implant (PPI) pointing to important technical aspects about this therapeutic option considering special populations.

The author conducted a critical review of all relevant publications from Medline and Embase databases and included a brief review of surgical challenges and a practical action-based set of recommendations on surgical options.

The risk of infection is still a matter and in diabetics it is more frequent and serious. Dr. Chung presented controversial numbers on ideal cut off value on HbA1c level and the lack of an evidence-based guideline published that precludes surgery above a certain value for HbA1c. He also stressed on the protective effect of antibiotic-impregnated implants (1) and high-volume surgeons (2). Postoperatively, diet and usual diabetes medications should be restarted as soon as possible, often under the guidance of a multidisciplinary team.

Other important special group is the one formed by spinal cord injury (SCI) men. Besides the fact that literature on the clinical outcomes of PPI surgery among neurogenic men is limited, Dr. Chung presented the question of which would be the best option for SCI patients: inflatable three-piece or the malleable or semi-rigid prosthesis, since they are often physically handicapped with poor hand dexterity, limited range of mobility, and muscle fatigue. On the other hand, the lack of sensation among SCI men may predispose those with a malleable implant to have a delayed identification and presentation of prosthetic

complications (3). Discussion on the advantages and disadvantages between malleable and inflatable PPI should be conducted based on the patient's physical characteristics, sexual needs, and cost.

The author also approached corporal fibrosis (e.g., Peyronie's disease or priapism), and salvage PPI surgery, since those cases can pose a substantial technical challenge in terms of corporal dilation and they do have a greater risk of prosthetic complications, especially device infection and erosion.

REFERENCES

1. Mulcahy JJ, Carson CC 3rd. Long-term infection rates in diabetic patients implanted with antibiotic-impregnated versus nonimpregnated inflatable penile prostheses: 7-year outcomes. Eur Urol. 2011;60:167-72.
2. Lipsky MJ, Onyeji I, Golan R, Munarriz R, Kashanian JA, Stember DS, Stahl PJ. Diabetes Is a Risk Factor for Inflatable Penile Prosthesis Infection: Analysis of a Large Statewide Database. Sex Med. 2019;7:35-40.
3. Zermann DH, Kutzenberger J, Sauerwein D, Schubert J, Loeffler U. Penile prosthetic surgery in neurologically impaired patients: long-term followup. J Urol. 2006;175(3 Pt 1):1041-4; discussion 1044.

Valter Javaroni, MD

Departamento de Andrologia,
Hospital Federal do Andaraí Rio de Janeiro,
Rio de Janeiro, RJ, Brasil
E-mail: drjavaroni2000@yahoo.com.br

ARTICLE INFO

Valter Javaroni
https://orcid.org/0000-0003-3877-0601

Int Braz J Urol. 2020; 46: 461-2

UPDATE IN UROLOGY

MALE HEALTH

Vol. 46 (3): 463-464, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.05

Editorial Comment: Impact of the advent of collagenase clostridium histolyticum on the surgical management of Peyronie's disease: a population-based analysis

Sukumar S [1], Pijush DB [2], Brandes S [3]

[1] Department of Urology, Columbia University, New York, NY, USA; [2] Department of Urology, Department of Biostatistics, Columbia University, New York, NY, USA; [3] Chief, Reconstructive Urology, Given Foundation Professor of Urology, Columbia University Medical Center, New York, NY, USA

J Sex Med. 2020 Jan;17(1):111-116

DOI: 10.1016/j.jsxm.2019.09.022 | **ACCESS:** 10.1016/j.jsxm.2019.09.022

Valter Javaroni [1]

[1] Departamento de Andrologia, Hospital Federal do Andaraí Rio de Janeiro, Rio de Janeiro, RJ, Brasil

COMMENT

After the 2013 FDA approval of collagenase clostridium histolyticum (CCH) what was its impact on the use of surgical management of Peyronie Disease (PD) in United State? Dr. Sukumar and cols. from Columbia University hypothesized that with the introduction of CCH, surgery as a primary treatment modality for PD would be used less often.

The authors reviewed 547 men with PD registered in Statewide Planning and Research Cooperative System (SPARCS) that provides data on patients in the outpatient, inpatient, ambulatory, and emergency department setting in New York. All patients >18 years old with a diagnosis with PD who received surgical therapy (ST), defined as plaque excision/incision and grafting or plication, or injection therapy (IT) as a primary treatment between 2003 and 2016 were included.

Over the study period, surgical management was used less often as the primary procedure with a concurrent increase in use of IT ($P < .001$). On multivariable modeling, patients more likely to receive IT as treatment for penile curvature were younger, of higher socioeconomic status and presented to a surgeon with a high volume practice.

That trend should worry other countries were CCH could be approved? IMPRESS I and II data revealed that men treated with CCH showed a mean 34% improvement in penile curvature, representing a mean -9.3 ± 13.6 degree change per subject ($p < 0.0001$) (1) after eight injections.

It is also relevant the many changes in CCH original protocol were proposed since its launch. The combination of traction devices and CCH, for example, seems to be associated with significantly greater curvature and length improvements compared with CCH alone (2).

Finally, in the first cost-effectiveness comparison of treatment modalities for PD (CCH, traction device and surgery) where the success was defined as ≥20% improvement in curvature, CCH was (by far) the most expensive and was not the most effective (3).

REFERENCES

1. Gelbard M, Goldstein I, Hellstrom WJ, McMahon CG, Smith T, Tursi J, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. J Urol. 2013;190:199-207.
2. Alom M, Sharma KL, Toussi A, Kohler T, Trost L. Efficacy of Combined Collagenase Clostridium histolyticum and RestoreX Penile Traction Therapy in Men with Peyronie's Disease. J Sex Med. 2019;16:891-900.
3. Wymer K, Kohler T, Trost L. Comparative Cost-effectiveness of Surgery, Collagenase Clostridium Histolyticum, and Penile Traction Therapy in Men with Peyronie's Disease in an Era of Effective Clinical Treatment. J Sex Med. 2019;16:1421-32.

Valter Javaroni, MD

Departamento de Andrologia,
Hospital Federal do Andaraí Rio de Janeiro,
Rio de Janeiro, RJ, Brasil
E-mail: drjavaroni2000@yahoo.com.br

ARTICLE INFO

Valter Javaroni
https://orcid.org/0000-0003-3877-0601

Int Braz J Urol. 2020; 46: 463-4

UPDATE IN UROLOGY

PROSTATE CANCER

Vol. 46 (3): 465-466, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.06

Editorial Comment: A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer

Hugosson J [1], Roobol MJ [2], Månsson M [3], Tammela TLJ [4], Zappa M [5], Nelen V [6], et al.

[1] Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Göteborg, Göteborg, Sweden; [2] Erasmus Medical Centre, Rotterdam, The Netherlands; [3] Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Göteborg, Göteborg, Sweden; [4] University of Tampere, Faculty of Medicine and Life Sciences, Tampere, Finland; [5] ISPRO, Oncological network, Prevention, and Research Institute, Florence, Italy; [6] Provinciaal Instituut voor Hygiëne, Antwerp, Belgium

Eur Urol. 2019 Jul;76(1):43-51

DOI: 10.1016/j.eururo.2019.02.009 | **ACCESS:** 10.1016/j.eururo.2019.02.009

Felipe Lott [1]

[1] Instituto Nacional do Câncer – INCA, Rio de Janeiro, RJ, Brasil

COMMENT

This is the 16 years follow-up of the European Randomized study of Screening for Prostate Cancer (ERSPC) that was initiated in 1993 and previously published with 9, 11, and 13 years of follow-up (1-3). This trail try to elucidate the effect of regular prostate-specific antigen (PSA) screening on prostate cancer (PCa) mortality.

This paper shows that the absolute reduction in PCa mortality still increases with longer follow-up, while the relative risk reduction remains at 20% since the initial report (1-3). There is still a 41% excess incidence in the screening arm. The median follow-up from diagnosis is modest (8.8 years in the screening arm and 5.4 years in the control arm) given the natural course of PCa.

The number needed to diagnose for averting one PCa death was 18 in this update paper and was much higher in the previous ones.

This high level evidence publication shows that the absolute effect of screening on PCa mortality increases with longer follow-up.

REFERENCES

1. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360:1320-8. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med. 2012;366:981-90.
2. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014;384:2027-35.

Felipe Lott, MD

Instituto Nacional do Câncer – INCA
Rio de Janeiro, RJ, Brasil
E-mail: felipelott@hotmail.com

ARTICLE INFO

Felipe Lott
https://orcid.org/0000-0001-5678-5343

Int Braz J Urol. 2020; 46: 465-6

UPDATE IN UROLOGY

FEMALE UROLOGY

Vol. 46 (3): 467-468, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.07

Editorial Comment: Impact of preoperative urodynamics on women undergoing pelvic organ prolapse surgery

Glass D [1], Lin FC [2], Khan AA [3], Van Kuiken M [4], Drain A [5], Siev M [5], Peyronett B [5], Rosenblum N [5], Brucker BM [5], Nitti VW [4]

[1] Department of Obstetrics and Gynecology, University of Chicago, Chicago, IL, USA; [2] Department of Urology, Division of Female Pelvic Medicine and Reconstructive Surgery, University of California Los Angeles, Los Angeles, CA, USA; 3 Department of Urology, Mayo Clinic, Scottsdale, AZ, USA; [4] Department of Urology, Division of Female Pelvic Medicine and Reconstructive Surgery, University of California Los Angeles, Los Angeles, CA, USA; [5] Department of Urology, Division of Female Pelvic Medicine and Reconstructive Surgery, New York University, New York, NY, USA

Int Urogynecol J. 2019; Aug 27. [Epub ahead of print]

DOI: 10.1007/s00192-019-04084-8 | **ACCESS:** 10.1007/s00192-019-04084-8

Cássio L. Z. Riccetto [1]

[1] Divisão de Urologia Feminina - Faculdade de Ciências Médicas da Universidade Estadual de Campinas – UNICAMP, Campinas, SP, Brasil

COMMENT

Pelvic organ prolapses (POP) are anatomical conditions of mainly surgical treatment. Thus, the role of urodynamics in POP preoperative assessment should be considered mainly as a tool for prediction of detrusor contractile function after POP surgical correction. Urodynamics also can be used as a complementary tool for the diagnose of occult urinary incontinence, although the same information can be reached through of a stress test with pessary or by reducing POP with a vaginal speculum. In fact the cost-effectiveness of urodynamics in preoperative POP workup still a matter of discussion (1).

In this retrospective study, the authors aimed to investigate the impact of urodynamic diagnosis in surgical planning of POP patients. For the analysis, preoperative indications for urodynamics were grouped in four categories: coexistence of urgency symptoms, mixed urinary incontinence, suspicion of occult urinary incontinence and coexistence of POP with symptoms of voiding dysfunction / incomplete emptying. They showed that among 316 women who underwent urodynamics prior to POP surgery, only 11 (3.2%) had a change in management and / or counseling not solely related to the presence or absence of occult stress incontinence. Furthermore, if patients with occult stress incontinence as an indication for urodynamics are excluded, management / counseling was carried out in only 9/146 (6.2%) of women. The authors concluded that excluding the mild utility in the diagnosis of occult stress incontinence, urodynamics had a limited role in POP management, despite highlight the usefulness of the urodynamic study in the pathophysiological diagnosis of voiding dysfunctions.

REFERENCES

1. Le Normand L, Cosson M, Cour F, Deffieux X, Donon L, Ferry P, et al. Clinical Practice Guidelines: Synthesis of the guidelines for the surgical treatment of primary pelvic organ prolapse in women by the AFU, CNGOF, SIFUD-PP, SNFCP, and SCGP. J Gynecol Obstet Hum Reprod. 2017;46:387-91.

Cássio L. Z. Riccetto, MD

Divisão de Urologia Feminina - Faculdade de Ciências Médicas da Universidade Estadual de Campinas – UNICAMP, Campinas, SP Brasil
E-mail: cassioriccetto@gmail.com

ARTICLE INFO

Cassio Riccetto
https://orcid.org/0000-0002-2428-3071

Int Braz J Urol. 2020; 46: 467-8

UPDATE IN UROLOGY

FEMALE UROLOGY

Vol. 46 (3): 469-470, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.08

Editorial Comment: The clinical role of LASER for vulvar and vaginal treatments in gynecology and female urology: An ICS/ISSVD best practice consensus document

Preti M [1], Vieira-Baptista P [2,3], Digesu GA [4], Bretschneider CE [5], Damaser M [5, 6, 7], Demirkesen O [8], et al.

[1] Department of Obstetrics and Gynecology, University of Torino, Torino, Italy; [2] Hospital Lusíadas Porto, Porto, Portugal; [3] Lower Genital Tract Unit, Centro Hospitalar de São João, Porto, Portugal; [4] Department of Urogynaecology, Imperial College Healthcare, London, UK; [5] Center for Urogynecology and Pelvic Reconstructive Surgery, Obstetrics, Gynecology and Women's Health Institute, Cleveland Clinic, Cleveland, Ohio; [6] Glickman Urological and Kidney Institute and Department of Biomedical Engineering Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio; [7] Advanced Platform Technology Center, Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio; [8] Faculty of Medicine, Department of Urology, Istanbul University Cerrahpaşa, Istanbul, Turkey

Neurourol Urodyn. 2019 Mar;38(3):1009-1023

DOI: 10.1002/nau.23931 | **ACCESS:** 10.1002/nau.23931

Cássio L. Z. Riccetto [1]

[1] Divisão de Urologia Feminina - Faculdade de Ciências Médicas da Universidade Estadual de Campinas – UNICAMP, Campinas, SP, Brasil

COMMENT

The rationale for the use of LASER, radiofrequency and focused ultrasound in Female Urology is based on the application of concentrated and controlled amount of energy to the subepithelial vaginal tissues, with the objective of triggering an inflammatory response that leads to collagen deposition and angiogenesis. It is theorized that these phenomena would determine the recovery of normal vaginal physiology. Although theoretically consistent, the real effectiveness of LASER, radiofrequency and focused ultrasound has not yet been adequately proven. However, in recent years, there has been a large proliferation of their indications, both in the medical and physical therapy field, for various conditions.

The present review was published by a panel of experts and followed the ICS White Paper about Standard Operating Procedures (1). According to the authors, the majority of studies available so far have not been randomized, were composed of small series, had short follow-ups and lacked control groups. The au-thors also noted that until now, studies on LASERS have been funded by industry and have not been com-pared with conventional treatments, so that the level of evidence is low to allow any recommendation for clinical use. In fact, most references from the review were categorized as level of evidence C or D, regardless the type of clinical indication. According to the authors, although tissue alterations have been described in some publications, they mostly consist of reparative tissue alterations after a thermal injury such that it is

difficult to establish a causal link between histological alterations and possible functional recovery.

Regarding urinary incontinence, six studies were included in the review, which comprised 19 to 205 patients without a control group, and response to treatment was assessed with short-term validated questionnaires (only one study referred to follow-up for 24 months).

Over the past 20 years, a myriad of treatments has been proposed for female urinary incontinence. Most of them were described as highly effective in initial publications, most of them with a short-term follow up. The advent of more developed scientific methods has shown that mid-urethral slings have proved to be reliable and safe long-term options for female incontinence. We expect that the use of laser and other energy sources in Female Urology diseases should soon be studied with the same quality standards.

REFERENCES

1. Salvatore S, Athanasious S, Yuen HTH, Karram M. LASER users' expert opinion in response to "The clinical role of LASER for vulvar and vaginal treatments in gynecology and female urology: An ICS/ISSVD best practice consensus document". Neurourol Urodyn. 2019;38:2383-4.

Cássio L. Z. Riccetto, MD

Divisão de Urologia Feminina - Faculdade de Ciências Médicas da Universidade Estadual de Campinas – UNICAMP, Campinas, SP Brasil
E-mail: cassioriccetto@gmail.com

ARTICLE INFO

Cassio Riccetto
https://orcid.org/0000-0002-2428-3071

Int Braz J Urol. 2020; 46: 469-70

UPDATE IN UROLOGY

FEMALE UROLOGY

Vol. 46 (3): 471-472, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.09

Editorial Comment: Does pre-operative urodynamics lead to better outcomes in management of urinary incontinence in women? A linked systematic review and meta-analysis

Lor KY [1], Soupashi M [1], Abdel-Fattah M [1], Mostafa A [2]

[1] *University of Aberdeen, Aberdeen, UK;* [2] *University of Aberdeen, Aberdeen, UK*

Eur J Obstet Gynecol Reprod Biol. 2020 Jan;244:141-153

DOI: 10.1016/j.ejogrb.2019.11.013 | **ACCESS:** 10.1016/j.ejogrb.2019.11.013

Cássio L. Z. Riccetto [1]

[1] *Divisão de Urologia Feminina - Faculdade de Ciências Médicas da Universidade Estadual de Campinas – UNICAMP, Campinas, SP, Brasil*

COMMENT

The usefulness of urodynamics in the evaluation of women with urinary incontinence is a recurring theme in the literature. Current is considered optional in index patients with typical stress incontinence (1) particularly if the first option is for physical therapy treatment. In the initial approach of patients with overactive bladder, whether wet or dry, is still considered to be expendable. On the other hand, its indication in patients with relapsed stress incontinence and mixed urinary incontinence is consensual (2). It is also found that few studies have included cost-effectiveness analysis among their outcomes. In this context, the authors presented three correlated systematic reviews and meta-analyzes of randomized controlled trials (RCTs) to compare the exclusive clinical versus the urodynamic use in three clinical scenarios: clinical pre--treatment of urinary incontinence, before surgical treatment of stress urinary incontinence and before invasive treatment of overactive bladder. Women with severe pelvic organ prolapse, previous continence surgery and neuropathic bladder were excluded from the analysis. Patient-reported and objective success post-treatment were the primary outcomes assessed and the secondary outcomes were adverse events, quality of life, sexual function and health economic measures (3).

Four RCTs compared urodynamics versus clinical evaluation only prior to non-surgical management of UI. Treatment consisted of. Meta-analysis of 150 women showed no evidence of significant difference in the patient-reported (P = 0.520, RR: 0.91, 95% Cl 0.69–1.21, I2 = 0%) and objective success rates (P = 0.470, RR: 0.87 , 95% Cl 0.59-1.28, I2 = n / a) between pelvic floor muscle training alone compared to pelvic floor muscle training with pharmacological therapy. Seven RCTs evaluated surgical management of SUI. The majority of women underwent mid-urethral tape procedures (retropubic or transobturator approach). Meta-analysis of 1149 women showed significant difference in patient-reported (P = 0.850, RR:

1.01, 95% CI 0.88-1.16, I2 = 53%) and objective success between groups (P = 0.630, RR: 1.02, 95% CI 0.95 - 1.08, I2 = 28%). There was no significant difference in incidence of voiding dysfunction, again urgency, and urinary tract infection between groups. No RCTs have been identified for invasive management of OAB. The authors concluded that there is limited evidence that routine urodynamics prior to non-surgical management of urinary incontinence or surgical management of stress urinary incontinence did not correlate to improvement in treatment outcomes, when compared to exclusive clinical evaluation. They also see the need for new well-designed clinical trials to evaluate the clinical and cost-effectiveness of routine urodynamics prior to surgical management of stress urinary incontinence and overactive bladder.

The multifactorial pathophysiological aspect of female urinary incontinence represents a challenge for any attempt to standardize its assessment and even treatment. Urodynamics is still the most reliable instrument for specialized study of lower urinary tract symptoms. An individualized approach is the current trend to determine its utility in specific patients.

REFERENCES

1. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. J Urol. 2019;202:558-63.
2. Kobashi KC, Albo ME, Dmochowski RR, Ginsberg DA, Goldman HB, Gomelsky A, et al. Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline. J Urol. 2017;198:875-83.
3. Serati M, Tarcan T, Finazzi-Agrò E, Soligo M, Braga A, Athanasiou S, Balzarro M. The bladder is an unreliable witness: The case for urodynamic investigations in female stress urinary incontinence. Eur J Obstet Gynecol Reprod Biol. 2020;244:35-7.

Cássio L. Z. Riccetto, MD

Divisão de Urologia Feminina - Faculdade de Ciências Médicas da Universidade Estadual de Campinas – UNICAMP, Campinas, SP Brasil
E-mail: cassioriccetto@gmail.com

ARTICLE INFO

Cassio Riccetto
https://orcid.org/0000-0002-2428-3071

Int Braz J Urol. 2020; 46: 471-2

UPDATE IN UROLOGY

RENAL CANCER

Vol. 46 (3): 473-473, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.10

Editorial Comment: The Emerging Role of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Systematic Review and Meta-Analysis

Correa RJM [1], Louie AV [2], Zaorsky NG [3], Lehrer EJ [4], Ellis R [5], Ponsky L [5], et al.

[1] Department of Radiation Oncology, London Regional Cancer Program, London, Ontario, Canada; [2] Department of Radiation Oncology, Sunnybrook Health Sciences Centre and the University of Toronto, Toronto, Ontario, Canada; [3] Department of Radiation Oncology, Penn State Cancer Institute, Hershey, PA, USA; [4] Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [5] University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Cleveland, OH, USA

Eur Urol Focus. 2019 Nov;5(6):958-969

DOI: 10.1016/j.euf.2019.06.002 | **ACCESS:** 10.1016/j.euf.2019.06.002

Stênio de C. Zequi [1]

[1] A. C. Camargo Cancer Center, Fundação Prudente, São Paulo, SP, Brasil

COMMENT

Historically, urologists do not recommend external beam radiotherapy for patients with renal cell carcinoma. But the progresses of radiotherapy have permitted the use of a high-precision stereotactic ablative radiotherapy in hypofractioned scheduling. It seems a therapeutic alternative of for elderly and frail patients which are not surgical candidates. The rational is to offer a single session of 26Gy or a short curse of 40Gy, delivered only on five sessions, in an outpatient treatment. The endpoints must be tumor size reduction or no tumoral progression, being interesting for symptomatic candidates. The results are acceptable and side effects are tolerable. In face recent reports in the literature, Correa and several international key opinion leaders, published this metanalysis, that evaluated 26 selected studies. Reading this article, we can ourselves updated on this therapeutic approach, destinated for a subgroup of patients that usually has almost none options of treatment.

Stênio de C. Zequi, MD

A. C. Camargo Cancer Center, Fundação Prudente, São Paulo, SP, Brasil
E-mail: steniozequi@gmail.com

ARTICLE INFO

Stenio C Zequi
https://orcid.org/0000-0003-1897-8085

Int Braz J Urol. 2020; 46: 473-3

UPDATE IN UROLOGY

RENAL CANCER

Vol. 46 (3): 474-475, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.11

Editorial Comment: Feasibility and safety of irreversible electroporation (IRE) in patients with small renal masses: Results of a prospective study

Buijs M [1], Zondervan PJ [2], de Bruin DM [3], van Lienden KP [4], Bex A [5], van Delden OM [4]

[1] Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [2] Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [3] Department of Biomedical Engineering and Physics, Academic Medical Center, Amsterdam, the Netherlands; [4] Department of Radiology, Academic Medical Center, Amsterdam, the Netherlands; 5 Department of Urology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Urol Oncol. 2019 Mar;37(3):183.e1-183.e8

DOI: 10.1016/j.urolonc.2018.11.008 | **ACCESS:** 10.1016/j.urolonc.2018.11.008

Stênio de C. Zequi [1]

[1] A. C. Camargo Cancer Center, Fundação Prudente, São Paulo, SP, Brasil

COMMENT

The options for therapy of patients presenting with small renal masses (SRM) is growing. Besides the partial nephrectomy or active surveillance, the percutaneous ablation performed through radiofrequency (FRFA) or cryoablation (CRYO) has been used in the last two decades. Beyond RFA and CRYO, new alternatives for ablation of kidney tumors has been proposed:

The percutaneous microwave ablation (PMWA), that is is no time-consuming procedure being also used also in complex cystic masses. Shapiro et al compared the use PMWA in 40 patients with T1b non metastatic renal cell carcinoma versus partial nephrectomy or radical nephrectomy. At end of study, complications were low, and functional and oncologic results were similar to surgical cases (the majority of the series). Patients undergone PMWA was older and presented more comorbidities. PMWA seems to be one more option for sick or old patients presenting tumors in pT1b stage, that are not included in traditional definition of SMR (< 4.0 cm).

Another recent option is irreversible electroporation, that has the first results published from a prospective Phase 2 Dutch trial, from Buijs et al. The treatment is based in repetitive electric pulses generated between needles (electrodes); that promotes destabilization on cellular membranes of target lesion, resulting

in cell death without promoting thermal damage of adjacent tissues. The procedure was safe, and painless, however required a long surgical anesthesia time (usually IRE is a quick procedure) , requiring a progressive skill of the teams evolved.

Both articles were on small casuistries, suggesting that these initial results are competitive with actual therapies. New technologies for ablation of renal tumors are welcome, in face the progressive increase of the diagnostic of SRM that has been concomitant with the widespread global population aging, that a risk factor for this malignance.

Stênio de C. Zequi, MD

A. C. Camargo Cancer Center, Fundação Prudente, São Paulo, SP, Brasil
E-mail: steniozequi@gmail.com

ARTICLE INFO

Stenio C Zequi
https://orcid.org/0000-0003-1897-8085

Int Braz J Urol. 2020; 46: 474-5

UPDATE IN UROLOGY

RENAL CANCER

Vol. 46 (3): 476-476, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2020.03.12

Editorial Comment: Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial

Bex A [1], Mulders P [2], Jewett M [3], Wagstaff J [4], van Thienen JV [1], Blank CU [1], et al.

[1] The Netherlands Cancer Institute, Amsterdam, the Netherlands; [2] Department of Urology, Radboud University Hospital, Nijmegen, the Netherlands; [3] Department of Urology, Princess Margaret Hospital, Toronto, Ontario, Canada; [4] Department of Oncology, Cardiff Hospital, Wales, United Kingdom

JAMA Oncol. 2019 Feb 1;5(2):164-170
DOI: 10.1001/jamaoncol.2018.5543 | **ACCESS:** 10.1001/jamaoncol.2018.5543

Stênio de C. Zequi [1]

[1] A. C. Camargo Cancer Center, Fundação Prudente, São Paulo, SP, Brasil

COMMENT

Authors presented data from a waited prospective study, SURTIME, which evaluated the best time of cytoreductive nephrectomy (CN)and target therapy with sunitinib in two groups: CN performed before sunitinib versus Upfront CN followed by the therapy. Despite its low number of recruited patients (99) due a poor accrual (it was planned for 458 patients), authors found that the progression free survival at 28 weeks in intention to treat analysis, was similar in both groups. However, the overall survival was superior in patients on deferred surgical arm. This study was important in verify that the use of sunitinib before surgery can helps in identification of patients resistant to this drug and that probably will be not benefited with the surgery. On the other hand, a patients with satisfactory response to sunitinib can be maintained as suitable surgical candidates. Additionally, the patients on deferred CN arm received more frequently the drug in comparison the group of immediate nephrectomies. Although the results can influence our therapeutic decisions, caution in necessary: We must not to extrapolate these results for patients with no clear cell hystologies of kidney cancer, or for patients presenting with poor performance status or with central nervous system metastasis, since they were exclude from the SURTIME population. We do not know if the future, these findings will be replaced in similar way on trials that are using modern immunotherapy or using immunotherapy in combination with target therapies before or after cytoreduction. Let's wait for this new data.

ARTICLE INFO

Stênio de C. Zequi, MD

A. C. Camargo Cancer Center, Fundação Prudente,
São Paulo, SP, Brasil
E-mail: steniozequi@gmail.com

Stenio C Zequi
https://orcid.org/0000-0003-1897-8085

Int Braz J Urol. 2020; 46: 476-6

RADIOLOGY PAGE

Vol. 46 (3): 477-480, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0522

Bladder pseudo-tumor: case report of vesical tamm-horsfall protein deposit

Marcelo Langer Wroclawski [1],Willy Roberto Camargo Baccaglini [2], Cristiano Linck Pazeto [2], Luisa Emanuela Biseo Henriques [2], Alexandre Kiyoshi Hidaka [2], Felipe Ko Chen [2], Milton Borreli [1], Renne Zon Filippi [1]

[1] Hospital Israelita Albert Einstein, São Paulo, SP, Brasil; [2] Disciplina de Urologia, Faculdade de Medicina do ABC, Santo André, SP, Brasil

INTRODUCTION

Urothelial carcinomas (UC) are malignant tumors that correspond to more than 90% of the bladder tumors (1). The main sign of UC is hematuria, however with the routine use of imaging exams, more patients are being diagnosed whilst asymptomatic. On ultrasonography (US), UCs present as a focal bladder wall thickening and/or a polypoid lesion (2).

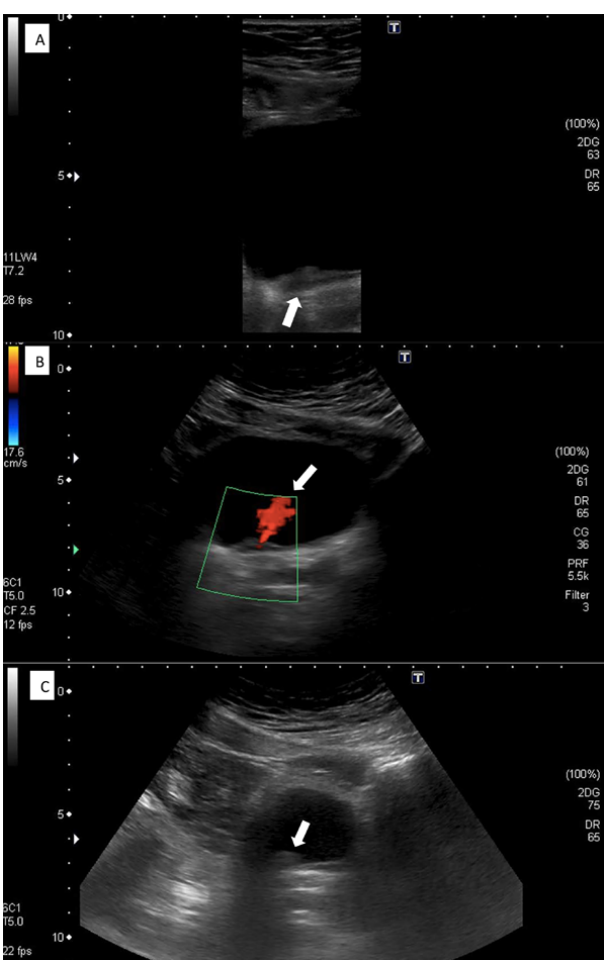
Nevertheless, these findings may be due to several other malignant and non-malignant differential diagnoses, such as nephrogenic adenoma, inverted papilloma, leiomyoma, amyloidosis, glandular cystitis, endometriosis, bladder xanthoma, among others (3-6). Cystoscopy is the gold standard procedure to investigate patients with suspicion of any bladder neoplasia.

Our objective is to report a case of Tamm--Hosrsfall protein deposit in the bladder wall, mimicking a vesical UC.

CASE REPORT

A 51-year-old asymptomatic man, with no history of hematuria, underwent to a routine US. The exam demonstrated a bladder with regular walls, except for an area of focal thickening and a nodular lesion in the bladder floor, close to the right ureteral meatus (Figure-1). Serum and urinary laboratory tests were normal.

Figure 1 – A: US with an area of focal thickening in the bladder floor (arrow); B: The focal thickening in the bladder floor is close to the ureteral meatus (arrow show the ureteric jet in US doppler); C: Nodular lesion in the bladder floor, close to the focal thickening (arrow).



Cystoscopy found three elevated lesions in the right lateral vesical wall, each one with about 0.5cm, all of which with intact mucosa. Additionally, there was an ipsilateral ulcerated peri-meatal lesion (Figure-2). All lesions were cold-cup biopsied and the pathological analysis revealed deposition of an eosinophilic proteinaceous substance throughout the mucosa and around the vessels. This was also associated with a mixed inflammatory process at the lamina propria, without evidence of cellular atypia (Figures 3 and 4). The search for infectious agents and amyloid protein (red-congo) were negative. The findings led to the diagnosis of Tamm-Horsfall protein deposition (THP). The patient remained asymptomatic and had no complications following the procedure.

DISCUSSION

The THP is a high molecular weight glycoprotein synthesized in the ascending portion of the Henle loop, and in the distal convoluted tubule. THP is abundant in normal human urine. Its actual physiological function remains unknown, but there is a hypothesis about a possible protective factor against urinary tract infections, lithogenesis, and some nephropathies (7-9).

The etiology for THP deposit is still unclear, however it is most likely related to mucosal changes, such as inflammation and necrosis (7-9).

A series of three patients with atypical THP mimichking tumor at the peri-pelvic and peri-renal fat tissues has been reported. In addition to the initial bladder carcinoma diagnostic hypothesis, renal pelvic neoplasia and urinary tuberculosis were also suspected (10). Another report presented a patient with a ureteral lesion associated with hydronephrosis, which suggested a tumor, but exactly like our case, histology favored THP deposition (11).

A large study consisting of 247 bladder biopsies and 15 specimens of cystectomy identified the presence of THP deposition in the bladder tissue in 18 cases (6.9%). The cystectomy cases presented positive biopsies for THP deposition in 60% of the patients, higher than isolated biopsies (3.6%). The author describes a typical pathological finding characterized by whitish masses with discrete eosinophilic deposition (12). However, our patient, beyond the THP deposits mimicking a bladder tumor, did not present any other bladder pathology or symptoms.

There are reports that have identified association between bladder wall THP deposition

Figure 2 (cystoscopy) – A) right peri-meatal region, which is evidencing ulcerated lesion (thick arrow) and lesions elevated with intact mucosa (narrow arrow); B) Image focused on elevated lesions (thick arrow); C) image focused on ulcerated lesion.

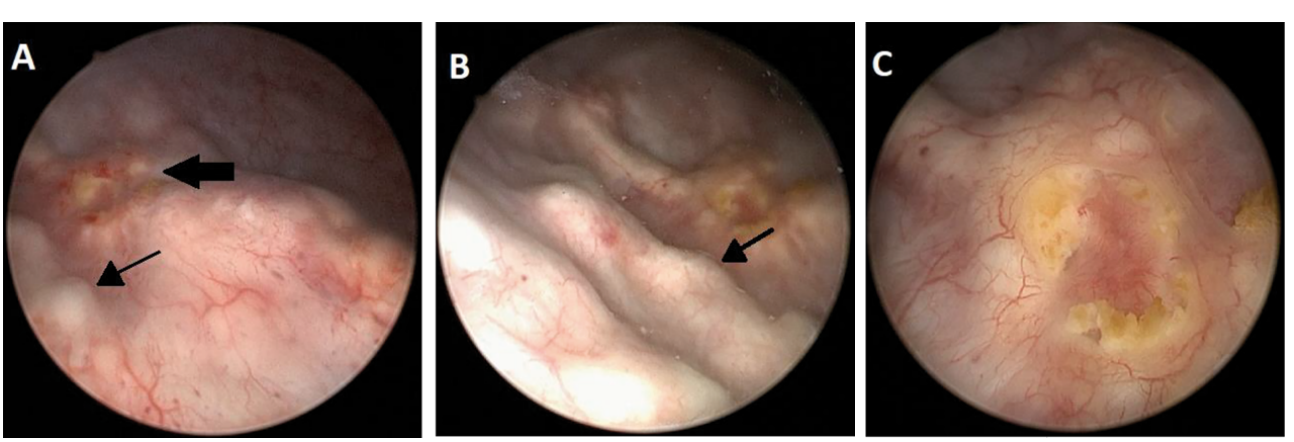


Figure 3 – Hematoxylin and Eosin (H&E) stain - Bladder biopsy: deposits of eosinofilic material in the lamina propria (arrows).

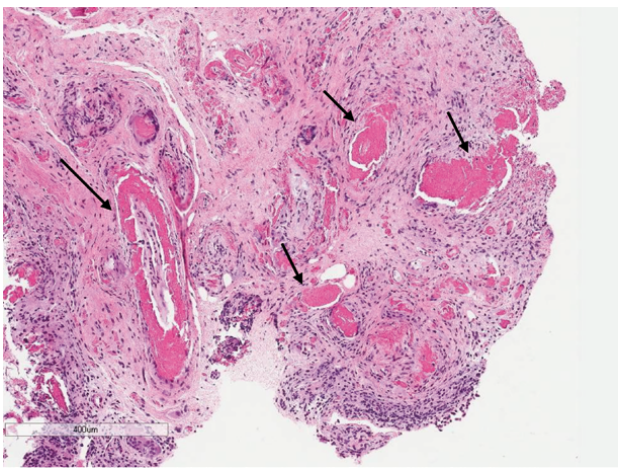
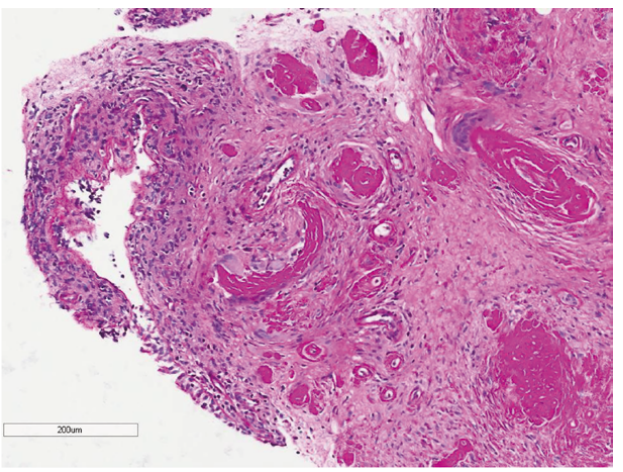


Figure 4 – Periodic Acid Schif (PAS) stain: eosinofilic material deposits strongly positive by the PAS stain.



and interstitial cystitis (13, 14). Additionally, patients with interstitial cystitis have been reported to have changes in THP when compared to control groups.

Our case demonstrates that THP deposition in the bladder may be one of the differential diagnoses for bladder lesions, mainly when the lesion does not have the usual papillary aspect and appears to be in a sub-urothelial layer.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wong MCS, Fung FDH, Leung C, Cheung WWL, Goggins WB, Ng CF. The global epidemiology of bladder cancer: a joinpoint regression analysis of its incidence and mortality trends and projection. Sci Rep. 2018;8:1129.
2. Lee CH, Tan CH, Faria SC, Kundra V. Role of Imaging in the Local Staging of Urothelial Carcinoma of the Bladder. AJR Am J Roentgenol. 2017;208:1193-205.
3. Sakatani T, Adachi Y, Sakaida N, Atsuta T, Magaribuchi T, Taki Y, et al. Nephrogenic adenoma in elderly patients: Three case reports. Mol Clin Oncol. 2016;5:253-6.
4. Veiga RS, Cassis J, Oliveira P, Lopez-Beltran A. Inverted Papilloma of the Bladder Coexisting with Urothelial Carcinoma. A Case Report. Anal Quant Cytopathol Histpathol. 2016;38:52-6.
5. Almouhissen T, Badr H, Alessa N, Nassir A. Bladder leiomyoma in male patient presenting with renal oncocytoma: Are the two conditions related? Urol Ann. 2016;8:397-9.
6. Raghavendran M, Venugopal A, Kaushik VN. Urinary Bladder Xanthoma - Is Immunohistochemistry Necessary? Urol Case Rep. 2016;8:36-7.
7. Weichhart T, Zlabinger GJ, Säemann MD. The multiple functions of Tamm-Horsfall protein in human health and disease: a mystery clears up. Wien Klin Wochenschr. 2005;117:316-22.
8. Säemann MD, Weichhart T, Hörl WH, Zlabinger GJ. Tamm-Horsfall protein: a multilayered defence molecule against urinary tract infection. Eur J Clin Invest. 2005;35:227-35.
9. Stein P, Rajasekaran M, Parsons CL. Tamm-Horsfall protein protects urothelial permeability barrier. Urology. 2005;66:903-7.
10. Devouassoux-Shisheboran M, Bouvier R, Roux MG, Marechal JM, Vauzelle JL. Ectopic deposits of Tamm-Horsfall protein. A psuedo-tumoral lesion. Ann Pathol. 1994;14:41-4.
11. Ivančič AK, Volavšek M. Tumor-like Accumulation of Uromodulin (Tamm-Horsfall Glycoprotein) in the Ureter. A Case Report of a Possible Diagnostic Pitfall. Anal Quant Cytopathol Histpathol. 2015;37:326-9.

12. Truong LD, Ostrowski ML, Wheeler TM. Tamm-Horsfall protein in bladder tissue. Morphologic spectrum and clinical significance. Am J Surg Pathol. 1994;18:615-22.
13. Bade JJ, Marrink J, Karrenbeld A, van der Weele L, Mensink HJ. Increased urinary levels of Tamm-Horsfall glycoprotein suggest a systemic etiology of interstitial cystitis. J Urol. 1996;156:943-6.
14. Parsons CL, Shaw T, Berecz Z, Su Y, Zupkas P, Argade S. Role of urinary cations in the aetiology of bladder symptoms and interstitial cystitis. BJU Int. 2014;114:286-93.

Correspondence address:
Marcelo Langer Wroclawski, MD, PhD
Hospital Israelita Albert Einstein
Rua: Iguatemi, 192 / 43-44
São Paulo, SP, Brasil
Cep: 01451-010
Fax: + 55 11 31682130
E-mail: urologia.marcelo@gmail.com

Submitted for publication:
August 11, 2019

Accepted after revision:
September 17, 2019

Published as Ahead of Print:
December 30, 2019

ARTICLE INFO

Marcelo Langer Wroclawski
http://orcid.org/0000-0001-6835-9085

Int Braz J Urol. 2020; 46: 477-80

VIDEO SECTION

Vol. 46 (3): 481-482, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2018.0584

Robotic conservative treatment for prostatourethrorectal fistula: original technique step by step

Michele Del Zingaro [1], Giovanni Cochetti [1], Gianluca Gaudio [1], Alberto Tiezzi [1], Alessio Paladini [1], Jacopo Adolfo Rossi de Vermandois [1], Ettore Mearini [1]

[1] *Department of Surgical and Biomedical Sciences, Urology Clinic, University of Perugia, Santa Maria della Misericordia Hospital Piazzale Menghini, Perugia, Italy*

ABSTRACT

Purpose: Prostatourethrorectal fistula (PURF) is an uncommon complication resulting from surgery, radiation or trauma (1). The most common therapeutic management is transperineal surgery (1). Transabdominal approach is less used and limited to large fistulae needing cystectomy and rectal resection (1). The aim of this study was to show an original robotic technique of conservative treatment for PURF.
Materials and Methods: A 75 years old man referred recurrent UTI, pneumaturia and urinary loss from rectum due to PURF arising after TURP performed after transvesical prostate adenomectomy. Cystogram, cystoscopy and MRI confirmed PURF. We used a robotic approach performing isolation, resection and suture of the fistulous tract on rectal and urethral side. Leak test was negative. We carried out an omental flap, positioned between rectum and prostatic urethra, and a temporary ileostomy without any bowel resection or urinary diversion.
Results: Operative time was 210 minutes, estimated blood loss 50ml. Oral feeding was restored at 48 hours. Bladder catheter was removed on the 15th post-operative day. Post-operative cystogram was negative. Post-operative complications were ileus and urinary tract infection. Hospital stay was 10 days. At 6 months follow-up, before temporary ileostomy closure, cystoscopy showed a totally re-epithelised fovea, and cystogram and CT enterography were negative.
Conclusions: Robotic conservative treatment of PURF seems to be safe and feasible (2, 3). Robotic approach allows accurate surgical dissection, through easier access to the rectal-prostatic plane, reducing the need for resection. To our knowledge, this is the first robotic conservative treatment for PURF reproducing the same steps of laparotomic approach with the advantages of minimally invasive technique (4).

ABBREVIATIONS

PURF = prostatourethrorectal fistula;
UTI = urinary tract infections;
TURP = transurethral resection of the prostate;
MRI = magnetic resonance imaging.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Giovanni C, Emanuele C, Roberto C, Alberto P, Emanuele L, Alessia C, et al. Laparoscopic conservative surgery of colovesical fistula: is it the right way? Wideochir Inne Tech Maloinwazyjne. 2013;8:162-5.
2. Cirocchi R, Cochetti G, Randolph J, Listorti C, Castellani E, Renzi C, et al. Laparoscopic treatment of colovesical fistulas due to complicated colonic diverticular disease: a systematic review. Tech Coloproctol. 2014;18:873-85.
3. Cochetti G, Del Zingaro M, Boni A, Cocca D, Panciarola M, Tiezzi A et al. Colovesical fistula: review on conservative management, surgical techniques and minimally invasive approaches. G Chir. 2018;39:195-207.
4. Giovanni C, Emanuele C, Francesco B, Emanuele L, Andrea B, Solajd P, et al. Laparoscopic conservative treatment of colo-vesical fistula: a new surgical approach. Int Braz J Urol. 2013;39:752; discussion 753.

ARTICLE INFO

Gianluca Gaudio
https://orcid.org/0000-0002-0082-1787

Available at: http://www.intbrazjurol.com.br/video-section/20180584_Del_Zingaro_et_al
Int Braz J Urol. 2020; 46 (Video #10): 481-2

Submitted for publication:
October 16, 2018

Accepted after revision:
August 16, 2019

Published as Ahead of Print:
December 30, 2019

Correspondence address:
Gaudio Gianluca, MD
Department of Surgical and Biomedical Sciences,
Urology Clinic, University of Perugia, Santa Maria della
Misericordia Hospital Piazzale Menghini 1
06156, Perugia, Italy
E-mail: gianluca.gaudio91@gmail.com

VIDEO SECTION

Vol. 46 (3): 483-484, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2018.0423

Laparoscopic Boari flap for treatment of benign mid-ureter stricture

Willian Eduardo Ito [1], Andre Fernando Tannouri Garbin [1], Marco Aurelio de Freitas Rodrigues [1], Silvio Henrique Maia de Almeida [1], Horacio A. Moreira [1]

[1] *Disciplina de Urologia, Universidade Estadual de Londrina, Centro de Ciências da Saúde, Londrina, PR, Brasil*

ABSTRACT

Introduction: Laparoscopic ureteral reconstructive surgery represents a real challenge for most of the urologists as it requires advanced skills. Impacted stones (>2 months) and endoscopic procedures are known major risk factors for ureteral strictures. Boari flap is a good alternative, due to the high recurrence of kidney stone disease, as it preserves the feasibility of ureteroscopy.
Material and Methods: We present a case of a 21-year-old female patient complaining of dull pain in the left flank, associated with vomiting and high-grade fever (39 degrees Celsius), for three days. Computed abdominal tomography demonstrated a 16mm ureteral stone in the left mid-ureter. Besides intravenous antibiotics, we installed a retrograde pigtail ureteral stent, a difficult procedure, due to extended length stenosis (retrograde pyelography, ~6cm). Two weeks after clinical improvement, we conducted a laparoscopic transperitoneal Boari flap for definitive treatment.
Results: Surgery had a duration of 169 minutes and 100mL of bleeding. The calculus was retrieved along with the fibrotic ureteral tissue. Psoas-Hitch was not needed and end-to-end flap-ureteral anastomosis was done using polyglactin 4.0 continuous sutures. Intraoperatively we had no significant issues. The patient was discharged three days post-operatively. Foley catheter was maintained for 14 days, and it was withdrawn after a cystography, ureteral stent was left for four weeks. Six weeks after the procedure, a urography was done, which showed a normal full bladder capacity and optimal drainage of the left kidney.
Conclusion: Laparoscopic Boari flap is feasible, resolutive and a safe minimally invasive technique for the treatment of mid-ureteral strictures.

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Willian Ito
https://orcid.org/0000-0002-1038-1375

Available at: http://www.intbrazjurol.com.br/video-section/ 20180423_Ito_et_al
Int Braz J Urol. 2020; 46 (Video #11): 483-4

Submitted for publication:
June 21, 2019

Accepted after revision:
August 16, 2019

Published as Ahead of Print:
December 30, 2019

Correspondence address:
Willian Eduardo Ito, MD
Disciplina de Urologia,
Univ. Estadual de Londrina,
Centro de Ciências da Saúde
Avenida Robert Koch, 60
Londrina, PR, 86038-440, Brasil
E-mail: willianito@hotmail.com

VIDEO SECTION

Vol. 46 (3): 485-486, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0074

Retroperitoneoscopic approach for highly complex posterior renal hilar tumors

Jose Luis Bauza [1], Valentí Tubau [1], Jorge Guimerà [1], Luis Ladaria [1], Carlos Aliaga [1], Pedro Piza [1], Enrique Pieras [1]

1 Department of Urology, Hospital Universitario Son Espases, Palma de Mallorca, Illes Balears, Spain

ABSTRACT

Objectives: To show our single-center experience in retroperitoneoscopic approach for highly complex posterior hilar tumors. Minimally invasive nephron sparing surgery for renal hilar tumors is extremely challenging due to their anatomic location, close to the main renal vessels and the collecting system (1). Transperitoneal approach is feasible, but highly complex because the anterior disposition of the vasculature. Retroperitoneal approach can easily provide access to the posterior hilar structures and the posterolateral surface of the kidney(2, 3).
Materials and Methods: We retrospectively reviewed our hilar renal tumor database and analyzed those in which a retroperitoneoscopic approach was chosen. The RENAL score was then calculated, and operative and ischemia times were recorded. We also collected the mean hospital stay and the presence of complications. Pathology reports and follow-up were also gathered.
Results: Five of our twelve highly complex hilar renal tumor patients were treated using a retroperitoneoscopic approach. Mean RENAL score was 10. Mean operative time was 135 minutes. Mean warm ischemia time was 14 minutes. Mean hospital stay was 4 days. We have recorded 2 complications. One patient required a transfusion and another presented with an urinary fistula which was treated by double J stent placement. The pathology report showed a clear cell renal cell carcinoma pT1a in most of the cases. Only one patient had a positive margin. To date, no recurrences have been noticed.
Conclusions: The treatment of complex renal hilar tumors in a minimally invasive fashion is highly challenging even in experienced hands. Retroperitoneal partial nephrectomy is feasible, safe and effective for the treatment of such lesions. Long-term oncologic outcomes of this approach are awaited.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sagalovich D, Dagenais J, Bertolo R, Garisto JD, Kaouk JH. Trifecta Outcomes in Renal Hilar Tumors: A Comparison Between Robotic and Open Partial Nephrectomy. J Endourol. 2018;32:831-6.
2. Fan X, Xu K, Lin T, Liu H, Yin Z, Dong W, et al. Comparison of transperitoneal and retroperitoneal laparoscopic nephrectomy for renal cell carcinoma: a systematic review and meta-analysis. BJU Int. 2013;111:611-21.
3. Kieran K, Montgomery JS, Daignault S, Roberts WW, Wolf JS Jr. Comparison of intraoperative parameters and perioperative complications of retroperitoneal and transperitoneal approaches to laparoscopic partial nephrectomy: support for a retroperitoneal approach in selected patients. J Endourol. 2007;21:754-9.

ARTICLE INFO

Jose Luis Bauza Quetglas
https://orcid.org/0000-0002-8955-483X

Available at: : http://www.intbrazjurol.com.br/video-section/20190074_Bauza_et_al
Int Braz J Urol. 2020; 46 (Video #12): 485-6

Submitted for publication:
February 06, 2019

Accepted after revision:
January 27, 2020

Published as Ahead of Print:
February 10, 2020

Correspondence address:
Jose Luis Bauza Quetglas, MD
Department of Urology
Hospital Universitario Son Espases
79, Valldemossa Rd
Palma de Mallorca, 70120, Spain
Telephone: + 34 608 688-560
E-mail: peplluis15@hotmail.com

VIDEO SECTION

Vol. 46 (3): 487-488, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0255

Ureteroscopic Resection of Ureteral Tumor

Eclair Lucas Filho [1], Luis César Zaccaro da Silva [1], Gilberto Saber [1]

[1] *Departamento de Urologia, Santa Casa de Misericórdia de Ribeirão Preto Ribeirão Preto, SP, Brasil*

INTRODUCTION

Accounting for only 5% of all renal and urothelial tumors, upper tract urothelial carcinoma (UTUC) is a rare genitourinary malignancy. Although management guidelines for UTUC recommend radical nephroureterectomy (RNU) with resection of a bladder cuff as the 'gold standard' treatment, the solitary kidney status after this procedure may lead to higher rates of dialysis, cardiovascular morbidity, and overall mortality. In an effort to mitigate these attendant risks, ureteroscopy (URS) and laser photoablation represent a valid treatment option for these patients with high comorbidities and/or low-risk disease and willing to undergo an intensive surveillance program.

Minimally-invasive endoscopic management of UTUC was first suggested for imperative cases as chronic kidney disease, solitary kidney, bilateral UTUC, and the good results obtained in terms of cancer control lead clinicians to offer this approach also to elective cases (patients with normal contralateral kidney).

The endoscopic treatment of upper tract UTUC coincided with the development and refinement of percutaneous renal surgery, ureteroscopy, and laparoscopy. These techniques can now be combined to provide histologic diagnosis of filling defects of the upper urinary tract, remove small to even large intraluminal lesions, or remove the distal ureter or the entire kidney and ureter with endoscopes alone.

CASE REPORT

We present the case of an 85-year-old male with asymptomatic gross hematuria for 1 month. The patient, despite advanced age, presented good performance status, and as comorbidities, presented cardiomyopathy, previous stroke (one year) and using Xarelto® (rivaroxaban), AAS, simvastatin and digoxin.

In the requested imaging tests, with better accuracy, the MRI revealed a lesion in the upper right ureter of a superficial and non-invasive character. Ureteroscopy then revealed a typical urothelial, pedunculated lesion of approximately 1cm, and was then resected by endoscopic resection with YAG-Holmium laser, and extraction of the specimen with Dormia's basket.

The surgery was performed without any complications, with a total time of 30 minutes and the patient was discharged on the first postoperative day, with a double-j stent, and asymptomatic.

Anatomopathological examination revealed superficial urothelial carcinoma (pTa) grade II/(high grade).

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Eclair Lucas Filho
https://orcid.org/0000-0002-5098-1017

Available at: http://www.intbrazjurol.com.br/video-section/20190255_Lucas_Filho_et_al
Int Braz J Urol. 2020; 46 (Video #13): 487-8

Submitted for publication:
April 17, 2019

Accepted after revision:
September 24, 2019

Published as Ahead of Print:
December 30, 2019

Correspondence address:
Eclair Lucas Filho, MD
Departamento de Cirurgia,
Fundação Hospital Adriano Jorge
Av. Carvalho Leal, 1778
Cachoeirinha, Manaus, AM, 69065-001, Brasil
E-mail: eclair.filho@gmail.com

VIDEO SECTION

Vol. 46 (3): 489-490, May - June, 2020
doi: 10.1590/S1677-5538.IBJU.2019.0148

Laparoscopic Pielolitotomy: An option for the management of pelvic kidney stones

Artur de Oliveira Paludo [1], Antonio Rebello Horta Gorgen [1], Marcio Araldi [1], Patric Machado Tavares [1], Nelson Sivonei Batezini [1], Tiago Elias Rosito [1, 2]

[1] Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil; [2] Universidade Federal do Rio Grande do Sul – UFRS, Porto Alegre, RS, Brasil

ABSTRACT

Introduction: Minimally invasive treatments such as extracorporeal shock wave lithotripsy and percutaneous nephrolithotripsy are standard procedures for the management of renal stones (1). However, renal position and rotation defects may significantly interfere in the results of these treatments (2). Open surgery has always been an option for these cases, but with the advancement of laparoscopy in the last decades, laparoscopic pielolitotomy has become a good alternative for approaching kidney stones in abnormal renal rotation and position (3).
Materials and methods: A 42-year-old male patient with a 2.2cm stone in the left pelvic kidney was submitted to laparoscopic pielolitotomy after extracorporeal schok wave lithotripsy failure and difficulty in access for percutaneous nephrolithotripsy. We did not have access to flexible ureteroscopy for this case.
Results: The surgical time was 150 minutes. An antegrade JJ stent was inserted and renal pelvic suture was performed with vicryl 4-0. There was no need for opioids and patient was discharged on the first postoperative day. The JJ stent was removed after 1 month, with complete resolution of the clinical symptoms.
Conclusions: Laparoscopic pielolitotomy is an excellent treatment alternative for patients with large stones in pelvic kidney.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ahangar S, Durrani AM, Qadri SJ, Patloo AM, Ganaie RG, Khan M. Laparoscopic trans-peritoneal pyelolithotomy in a pelvic kidney. Saudi J Kidney Dis Transpl. 2012;23:1254-7.
2. Hoenig DM, Shalhav AL, Elbahnasy AM, McDougall EM, Clayman RV. Laparoscopic pyelolithotomy in a pelvic kidney: a case report and review of the literature. JSLS. 1997;1:163-5.
3. Kamat N, Khandelwal P. Laparoscopic pyelolithotomy--a technique for the management of stones in the ectopic pelvic kidney. Int J Urol. 2004;11:581-4.

ARTICLE INFO

Artur de Oliveira Paludo
https://orcid.org/0000-0002-0701-3301

Available at: http://www.intbrazjurol.com.br/video-section/20190148_Paludo_et_al
Int Braz J Urol. 2020; 46 (Video #14): 489-90

Submitted for publication:
February 27, 2019

Accepted after revision:
August 16, 2019

Published as Ahead of Print:
December 30, 2019

Correspondence address:
Artur de Oliveira Paludo, MD
Hospital de Clínicas de Porto Alegre
Rua: Ramiro Barcelos, 2350/Sala 835
Porto Alegre, RS, Brasil
E-mail: arturpaludo@gmail.com

INTERNATIONAL
BRAZ J UROL

INFORMATION FOR AUTHORS

Manuscripts submitted for publication should be sent to:

Luciano A. Favorito, MD, PhD
Editor, International Braz J Urol

Submit your article here:
https://www.intbrazjurol.com.br

Manuscripts must be written in current English or Portuguese. Non-native English speakers should ask a native specialist in medical English for checking the grammar and style. Either American or British English may be used but should be consistent throughout the manuscript.

A submission letter signed by all authors must accompany each manuscript. This letter must state that: a)- the paper or portion thereof have not been previously published and are not under consideration by another Journal, b)- that all authors have contributed to the information or material submitted for publication, and that all authors have read and approved the manuscript, c)- that the authors have no direct or indirect commercial financial incentive associated with publishing the manuscript, d)- that the source of extra-institutional funding, specially that provided by commercial companies, is indicated, e)- that the study had been reviewed and approved by a certified Ethical Board or Committee, including the nmeber of the approval dociment and the date of the approval, f)- a non-plagiarism statement (I (We) declare that all material in this assignment is my (our) own work and does not involve plagiarism). g)- Clinical trials must be registered on any Clinical Trials Registry and the letter must bring the number of registration and the name of the registry. After accepted for publication, the manuscript will become property of the **International Braz J Urol.**

Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, must be clearly disclosed when submitting a manuscript for review. If accepted, a disclosure will be published in the final manuscript.

The requirements for authorship and the general rules for preparation of manuscripts submitted to the **International Braz J Urol** are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med, 126: 36-47, 1997). An electronic version of the Uniform Requirements is available on various websites, including the International Committee of Medical Journal Editors web site: www.icmje.org.

In response to the concerns of the editors of scientific medical journals with ethics, quality and seriousness of published articles, a Committee on Publication Ethics (COPE) was established in 1997 and a guideline document was published. The International Braz J Urol signed, approved, and follows the COPE guidelines. The Editor strongly encourages the authors to carefully read these guidelines before submitting a manuscript **(www.publicationethics.org.uk/guidelines or www.brazjurol.com.br**, vol. 26 (1): 4-10, 2000).

Peer Review – All submissions are subject to editorial review. Typically, each manuscript is anonymously forwarded by the Editor to 4 Reviewers (at least 2). If the Editor receives conflicting or inconclusive revisions, the manuscript is always sent to 1 or 2 additional Reviewers before the Editor's decision. If considered necessary by the Editor or by the Reviewers, statistical procedures included in the manuscript will be analyzed by a statistician.

The **International Braz J Urol** contains six sections: **Original Article, Review Article, Surgical Technique, Challenging Clinical Case, Radiology Page**

and **Video Section**. The articles should be written in Portuguese or English official orthography.

Abbreviations should be avoided, and when necessary must be specified when first time mentioned. Unusual expressions may not be used. A list of abbreviations must be provided at the end of the manuscript.

Every manuscript submitted to publication should have a cover page containing the title, short title (up to 50 characters), authors and institution. Up to six key words should be provided. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine **(http://www.nlm.nih.gov/mesh/meshhome.html)**. One of the authors should be designated as correspondent and the complete correspondence address, telephone and fax numbers and E-mail should be provided.

If any financial support has been provided, the name of the institution should be mentioned.

Original Article: Original articles should contain a Cover Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusions, References, Tables and Legends, each section beginning in a separate page and numbered consecutively. Original articles should cover contemporary aspects of Urology or experimental studies on Basic Sciences applied to urology. The manuscript text should contain no more than 2500 words, excluding the Abstract. The number of authors is limited to five. References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

Review Article: Review articles are accepted for publication upon Editorial Board's request in most of the cases. A Review Article is a critical and systematic analysis of the most recent published manuscripts dealing with a urological topic. A State of the Art article is the view and experience of a recognized expert in the topic. An abstract must be provided.

Surgical Technique: These manuscripts should present new surgical techniques or instruments and should contain Introduction, Surgical Technique, Comments and up to five References. An abstract must be provided. At least five cases performed with the technique must be included.

Challenging Clinical Case: These manuscripts should present relevant clinical or surgical situations which can bring or consolidate our understanding of genesis, natural history, pathophysiology and treatment of diseases.
Structure of the articles

Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario:** Description of case(s) relevant preceding and existing aspects;
- **Case(s) hypothesis and rational:** precepts, clinical and basic reasoning supporting the case(s) hypothesis and the raised scenario. Why is it important and is being reported?
- **Discussion and future perspectives:** what might it add and how does it relate to the current literature. 'Take-home message' - lessons learnt;
- **Table and/or Figure limits:** 2 (plates aggregating multiple images are encouraged) each exceeding table or figure will decrease 250 words of the full text;
- **Number of references:** 10-15.

Radiology Page: Will be published upon the Section Editor decision.

Video Section: The material must be submitted in the appropriate local, in the Journal's site, whe-

re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

ILLUSTRATIONS:

The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

ELECTRONIC SUBMISSION:

1) Do not embed the figures in the text, but supply them as separate files.
2) For Submitting Photographs Electronically, please:
Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, **not embed in Word or PowerPoint.**
3) For Submitting Line Artwork Electronically please note that:
Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
4) IMPORTANT - Avoid - Do Not

a) **DO NOT** embed the images in the text; save them as a separate file
b) **DO NOT** supply artwork as a native file. Most illustration packages now give the option to "save as" or export as EPS, TIFF or JPG.
c) **DO NOT** supply photographs in PowerPoint or Word. In general, the files supplied in these formats are at low resolution (less than 300 dpi) and unsuitable for publication.
d) **DO NOT** use line weights of less than 0.25 point to create line drawings, because they will nor appear when printed.

TABLES: The tables should be numbered with Arabic numerals. Each table should be typed on a single page, and a legend should be provided for each table. Number tables consecutively and cites each table in text in consecutive order.
REFERENCES: The References should be numbered following the sequence that they are mentioned in the text. The references should not be alphabetized. They must be identified in the text with Arabic numerals in parenthesis. Do not include unpublished material and personal communications in the reference list. If necessary, mention these in the body of the text. For abbreviations of journal names refer to the "List of Journals Indexed in Index Medicus" (http://www.nlm.nih.gov). The authors must present the references according to the following examples; the names of **all authors** must be included; when exist more than six authors, list the first six authors followed **by et al.** The **initial** and the **final** pages of the reference should be provided:

Papers published in periodicals:

▪ Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

▪ Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

▪ Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:

▪ Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

THE EDITORS SUGGEST THE AUTHORS TO OBSERVE THE FOLLOWING GUIDELINES WHEN SUBMITTING A MANUSCRIPT:

The **Ideal Manuscript** may not exceed 2500 words.

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

NOTE:

Recent issues of the International Braz J Urol must be observed concerning the presentation form of the manuscript.

INTERNATIONAL
BRAZ J UROL

MANUSCRIPT CHECKLIST

The authors should observe the following checklist before submitting a manuscript to the **International Braz J Urol**

- The sequence of manuscript arrangement is according to the Information for Authors.
- The Article is restricted to about 2,500 words and 6 authors.
- Abbreviations were avoided and are defined when first used and are consistent throughout the text.
- Generic names are used for all drugs. Trade names are avoided.
- Normal laboratory values are provided in parenthesis when first used.
- The references were presented according to the examples provided in the Information for Authors. The references were numbered consecutively, following the sequence that they are mentioned in the text. They were identified in the text using Arabic numeral in parenthesis. The names of all authors were provided. When exist more than six authors, list the first sixauthors followed by et al. The initial and the final pages of the reference should be provided. The number of references must be accordingly to the informed in the Instructions for Authors, depending on the type of manuscript.
- The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.
- Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.
- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
- A corresponding author with complete address, telephone, Fax, and E-mail are provided.
- A submission letter and a disclosure form, signed by all authors, are included.
- The authors should included written permission from publishers to reproduce or adapt a previously published illustrations or tables.
- **Conflict of Interest** – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, is clearly disclosed in the manuscript.
- **Check that each figure is cited in the text. The illustrations are not merged in the text.**
- The photographs are supplied as TIFF or JPG files and saved at a resolution of 300 dpi (dots per inch) at final size.
- The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not **embed in Word or PowerPoint.**
- A list of abbreviations is provided.