ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY
VOLUME 40, NUMBER 6, NOVEMBER – DECEMBER, 2014

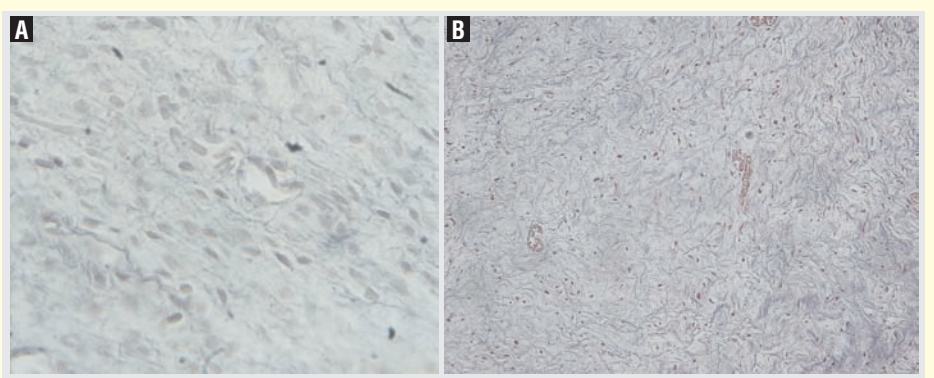

Figure 2 - A) Photomicrograph of a male fetus with 15 weeks post-conception with both testes situated in the abdomen. A low concentration of collagen and elastic fibers in the gubernaculum can be observed (HE, 400x). B) Photomicrograph of a male fetus with 35 weeks post-conception with both testes situated in the scrotum. A condensation of the gubernaculum with a large amount of collagen and elastic fibers can be observed. Masson's trichrome, 200x.

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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
DRQ Gráfica e Editora Ltd.

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

CAPES

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, has a circulation of 6,000 copies per issue and is published 6 times a year (bimonthly, starting in January - February).
The issue date is up to 2 weeks after the month of issuefor the hard copy and up to 1 week after the month of issue for the electronic version.

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, ISI - Current Contents / Clinical Medicine and Science Citation Index Expanded.

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EDITOR'S COMMENT

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doi: 10.1590/S1677-5538.IBJU.2014.06.01

Sexual stereotypes in Medicine

Sexuality is a doubtless complex topic. Several personal experiences, social issues, cultural characteristics, psychosocial interpretations, medical literature, philosophical demands and ethical aspects, among others, are related to it and all are equally important. Due to its multidimensional characteristic, sexuality is omnipresent in life of all human beings in spite of the time consumed to formalize its specific study. Many disciplines and varied focus have considered sexuality under different points of view, due to its rich characteristics, exposing its complexity.

In spite of the diversity of approaches, there are nowadays many consensus that are considered necessary, and many are associated to two main questions: a. science evolution, that provides more reliable and precise answers and not opinions, and b. definition, declaration, sexual rights defense and promotion in order to achieve sexual health. But sometimes the dialogue between these two central aspects may not translate into a specific practical expression. I want to refer to this topic, through a particular question.

Last October, São Paulo housed the International Congress of Sexual Medicine. In some presentations – based on the biomedical paradigm (1) as well as those related to bio-psycho-social aspects (2) presented some data using images that were a form of visual stimulation of the researched information. I want to comment the use of sexual stereotyped images of "heterosexual young whites with a modeled beauty pattern". We must remember that "simple stereotypes may be oppressive and when they are prescriptive, they may be immoral and illegal, or, what should people do or not be allowed to? (3).

This use of stereotyped images reminds me of two important medical questions related to:

a) Ethics: some argue that medical ethics presents two very specific sides, with antagonistic aspects, even if not opposites. The first side, ethics, that we call "E", deals with important practical questions that achieve rapidly a consensus, even only for being political correct. Health bioethics relates to controversial strong topics, far away from day-by-day practice. The second is related to daily activities, and almost always deals with practical aspects of consultation, conversation and sharing: "everyone has his own conscience".

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b) Scientific aspects: in order to explain these aspects, we must wonder if sexuality in centered in genitals or if it is related to multiple and multidimensional aspects of the human being.

It is not a simple moral stance. I think the ethical question has epistemological characteristics that we include when we use certain images in a particular context. I would like to ask readers if when we select sexual images for our presentations do we really follow any process of selection according to our idea of sexuality? We ourselves have the answer to that question, as with all ethical questions. And we must figure out that this is a way of our expression.

In relation to the second, the situation is far more complex, since in this particular we cannot deny evidences. The question is more specific, controversial and disturbing: which value do we assign to sexual stereotypes as causes of sexual health disturbances? In order to analyze this aspect, we must recall the theory of sexual scripts by Gagnon & Simon, that stated that "they provide an useful landmark for the understanding of the sexual roles of men, women, boys and girls during intercourse" (4). Secondly, we must stress the importance of health promotion – in our case sexual health – for the medical practice, regardless the personal effort. Modern medicine usually investigates troublesome situations regarding sexual function, seeking answers to specific sexual disorders to determine better diagnosis and to propose better treatments, in order to promote health allowing people a better routine life. "Multiple approaches for promotion of sexual health are necessary due to biological, psychological and sociological aspects of people's life" (5). Now I return to my almost rhetorical question: can we at present sustain sexual stereotypes being ourselves health care professionals?

I want to point out that the proposed sexual rights that we profess must not be lightly used but be applied according to our attitudes, skills and messages. I believe that health care is systematically and routinely pursuing this goal, particularly sexual science in this new millennium.

As health care providers, it is useful to remind us that we not always have the necessary resources to attend all possible demands. There must be a Hippocratic principle to guide and stimulate us: "some patients, although aware of the sensitive condition, regain health through the kind interaction with their doctors". An effective example of this is to avoid stereotypes to be used and reinforced, avoiding damage to the people.

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REVIEW ARTICLE

Vol. 40 (6): 722-729, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.02

The importance of the gubernaculum in testicular migration during the human fetal period

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ABSTRACT

Objectives: The objective of this review is to study the role of the gubernaculum in the testicular migration process during the human fetal period.
Materials and Methods: We performed a descriptive review of the literature about the role of the gubernaculum in testicular migration during the human fetal period.
Results: In the first phase of testicular migration, the gubernaculum enlarges to hold the testis near the groin and in the second phase the gubernaculum migrates across the pubic region to reach the scrotum. The proximal portion of the gubernaculum is attached to the testis and epididymis and the presence of multiple insertions in the distal gubernaculum is extremely rare. The presence of muscle and nerves in the human gubernaculum is very poor. The gubernaculum of patients with cryptorchidism has more fibrous tissue and less collagen and when the patients are submitted to hormonal treatment, the gubernaculum components alter significantly.
Conclusions: The gubernaculum presents significant structural modifications during testicular migration in human fetuses.

ARTICLE INFO

Key words:
Testicular Diseases; Cryptorchidism; Embryology; Fetus; Testis

Int Braz J Urol. 2014; 40: 722-9

Submitted for publication:
June 20, 2014

Accepted after revision:
October 31, 2014

INTRODUCTION

Testicular migration is a complex process of relevant importance for the comprehension of cryptorchidism. During the human fetal period, the testes migrate from the abdomen to the scrotum, traversing the abdominal wall and the inguinal canal between the 15th and the 28th week post-conception (WPC) (1-4). Several theories have been developed to explain testicular migration. The most accepted ones are: (a) the increase in the intra-abdominal pressure (5); (b) the development of the epididymis, spermatic vessels, deferent ducts and inguinal canal (6-8); (c) the stimulus originating in the genito-femoral nerve (9); (d) the hormonal stimulus originating in the placental gonadotrophin and the testosterone produced by the fetal testes (10); and (e) the gubernaculum's development (1, 11). The gubernaculum seems to be the most important anatomical structure in the testicular migration process, by means of contraction and shortening, thus imposing traction strength on the testis (1).

The objective of this review is to study the role of the gubernaculum in the process of testicular migration during the human fetal period.

MATERIAL AND METHODS

In this study we carried out a review of the Pubmed, Embase and Scielo databases about the role of the gubernaculum in testicular migration published in the past 40 years by using the key expressions "gubernaculum testis" and "testicular migration". We found several papers in these databases and we included only papers

in English and excluded case reports, editorials and opinions of specialists.

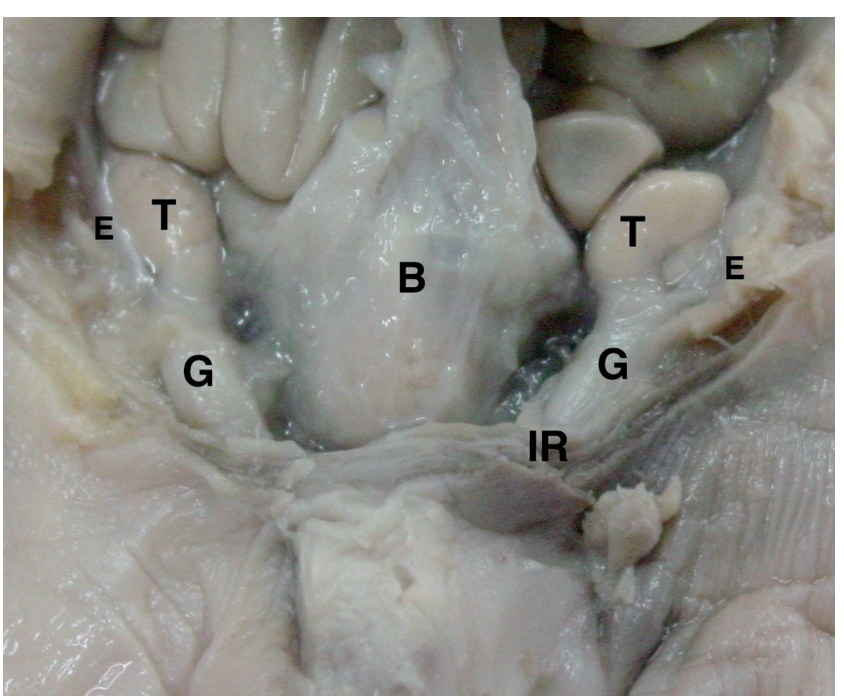
RESULTS

Testicular migration happens in two distinct phases: the first phase corresponds to the testicular migration from the abdomen to the internal inguinal ring, and the second phase corresponds to the transition of the testes through the inguinal canal until their definitive arrival at the scrotum (1-3). In the first phase, the gubernaculum enlarges to hold the testes near the groin, regulated by insulin-like 3 (INLS-3) (12, 13). INSL-3 is secreted by the Leydig cells and controls gubernaculum swelling via its receptor, LGR8 (leucine-rich repeat containing G protein-coupled receptor 8, also known as GREAT or relaxin receptor 2), a process resulting in thickening of the gubernaculum because of increases in water, glycosaminoglycan and hyaluronic acid content (11-14) (Figure-1).

In the second phase of testicular migration, the gubernaculum migrates across the pubic region to reach the scrotum. The androgens stimulate growth and differentiation of the muscular part of the gubernaculum bulb, which facilitates the movement of the gubernaculum through the inguinal region by the traction resulting from this growth (6, 12, 15, 16). The gubernaculum has its own nerve supply, the genito-femoral nerve (GFN), descending on the anteromedial surface of the psoas muscle from L1-L2 segments (17). The second phase of testicular descent is regulated by androgens and calcitonin gene-related peptide (CGRP), released by the sensory nucleus of the genitofemoral nerve (GFN) (10, 18). In rodents, the active proliferation of the gubernacular tip and cremaster muscle, the muscle's rhythmic contraction, and the chemotactic gradient provided by the CGRP together result in migration of the testes into the scrotum. The importance of this mechanism is corroborated by experimental models where the sectioning of the genitofemoral nerve leads to cryptorchidism (1, 15, 18).

The moment when testicular migration begins is controversial. Backhouse (2) reported that

Figure 1 - Image of a male fetus aged 22 weeks post-conception with both testes situated in the abdomen. The abdominal wall was dissected to show the position of the testis (T) above the internal ring (IR). The figure shows the gubernaculum (G) and the bladder (B).



this process starts at about the 24th week post-conception, while Heyns (3) and Sampaio & Favorito (4) described cases where the migration process started as early as the 17th week. An aspect that various authors report is that the passage of the testis through the inguinal canal occurs very quickly (2-4). Heyns (3) found only 2.6% of the testes examined in his sample located in the inguinal canal, while Sampaio & Favorito (4), in a sample of 71 human fetuses, found 20.5% of the testes located there. Furthermore, 73.3% of these testes were in fetuses with ages between 21 and 25 WPC, indicating that in this period the migration through the inguinal canal intensifies. In the same study, all the fetuses older than 30 weeks already showd the testes in the scrotum. Other authors, however, report that the testicular migration is only completed after the 32nd week post-conception (1-3).

Gubernaculum Testis

The gubernaculum starts to develop in the human fetus during the sixth week of gestation, the same period when the germinative cells are arriving at the genital ridge (1, 19).

In the eighth week of gestation, the testis and mesonephros are linked to the posterior abdomen wall by a peritoneal fold. As the mesonephros degenerates, the portion of this fold cranial to the testis, called the diaphragmatic ligament, also degenerates, turning into the cranial portion of the gonadal mesentery. This structure is called the caudal gonadal ligament, which gives rise to the gubernaculum testis (3, 19).

Cranially, the gubernaculum approaches the mesonephric duct, while distally it approaches the inguinal region. At this moment, the future inguinal canal is still only a space in the musculature of the anterior abdominal wall, where only mesenchyme tissue exists. In this region, the genital branch of the genitofemoral nerve crosses the abdominal wall and descends to the scrotum where it will innervate the cremaster muscle, and subsequently, in the caudal to cranial direction, will provide the nerve supply to the gubernaculum (1, 2, 6, 19).

Around the eight week of gestation, a portion of the epithelium starts a small invagination from the coelomic cavity, across from the gubernaculum, slowly penetrating its mesenchymal substance. This invagination occurs bilaterally and is considered as the start of the vaginal process. Some authors consider this phenomenon to be "active", involving the invasion of the gubernaculum by mesothelial cells (19), while others advocate that this phenomenon is "passive" and secondary to the increase in intra-abdominal pressure (6, 20).

The growth of the vaginal process divides the gubernaculum into three parts: (a) the main gubernaculum, which corresponds to the portion covered by the visceral layer of the peritoneum of the vaginal process; (b) the vaginal gubernaculum, which corresponds to the portion that externally surrounds the parietal portion of the vaginal process, and (c) the infra-vaginal gubernaculum, that corresponds to the caudal region of the gubernaculum, which has not been invaded by the vaginal process (19-21).

Both the gubernaculum and vaginal process change in harmony during testicular migration. The maintenance of this undifferentiated mesenchyme along the inguinal canal and scrotum is essential for the downward extension of the vaginal process to occur, during which it follows the pathway created by dilation of the gubernaculum, forming the canal through which the testis will reach the scrotum (1, 2, 19, 21).

The gubernaculum is a cylindrical structure, covered by a peritoneum on all sides except the posterior, where the testicular vessels and vas deferens pass. Macroscopically, it looks like the Wharton's jelly of the umbilical cord. Histologically, it is composed of undifferentiated cells with elongated shape, surrounded by a large quantity of extracellular material, where it is impossible to identify smooth or striated muscle cells except in its distal end and in the peripheral portion (22).

Proximal Gubernaculum

The proximal portion of the gubernaculum is adhered to the lower pole of the testis and to the epididymis. During testicular migration, these structures move through the inguinal canal as a single unit (2, 19, 23). According to Johansen & Bloom (24), in this situation the proximal gubernaculum is always adhered to the end of the vaginal

process. Jackson (25), studying 60 boys submitted to orchiopexy, found the gubernaculum adhered to the lower testicular pole in all cases, but did not mention its relationship with the epididymis.

Other studies have shown that changes in the proximal insertion of the gubernaculum are associated with epididymal anomalies and can contribute to the occurrence or cryptorchidism (26). Attah & Hutson (6), in a study with rats, demonstrated the importance of the integrity of the proximal portion of the gubernaculum for proper testicular migration. The proximal portion is important by uniting the scrotal region and serves as a guide for testicular migration. In this experiment, the authors performed transection of the proximal gubernaculum. After this procedure, the testicular migration was only completed in 26 of the 70 rats (37%), and of these animals 24 showed testicular torsion. The results of this study indicate that the proximal gubernaculum is important both to guide testicular migration and to limit the mobility of the testes and prevent testicular torsion.

Abe (27), in a study of 44 patients with cryptorchidism, found an elongated epididymis in 42.5% of the cases. Among the patients with elongated epididymis, alterations in the proximal gubernaculum were found in 73.9% of the cases. In other study of human fetuses, the authors found a low rate of epididymal anomalies (2.75%) (28).

Distal Gubernaculum

The insertion site of the gubernaculum during testicular migration is variable. Studies have shown that in the period before the end of testicular migration, the distal gubernaculum is not firmly attached to the scrotum (1, 5, 18). While the testis is located inside the abdomen, the gubernaculum is firmly attached to the inguinal canal (1,18).

The insertion site of the distal gubernaculum is one of the factors involved in testicular ectopia (29). Several papers have reported that the distal gubernaculum has six extensions: abdominal, pubopenile, femoral, perineal, contralateral scrotal and scrotal (1, 5, 29, 30). It is speculated that these branches of the distal gubernaculum exist during the beggining of fetal development and disappear during testicular migration (1, 3, 29, 30). If any of these extensions of the distal portion persist, the individual can develop testicular ectopia (30).

Various theories have been proposed to explain testicular ectopia. The most accepted are: (a) failure of the gubernaculum to dilate the inguinal canal, enabling the testis to migrate through other pathways and not reach the scrotum (29); (b) invasion of the gubernaculum by abdominal wall fascias near the inguinal canal, blocking the passage of the testis to the scrotum and diverting it to ectopic sites (1, 30); and (c) the existence of multiple distal insertions of the gubernaculum testis, guiding the testis to the main ectopic sites (1, 2, 30).

The most accepted theory to explain testicular ectopia is the existence of multiple distal insertions of the gubernaculum. According to this theory, proposed by Lockwood in nineteenth century (29), the gubernaculum presents six distal insertion sites, in decreasing order of frequency: scrotal, interstitial (abdominal), femoral, perineal, transverse (contralateral scrotal) and pubopenile.

Multiple distal insertions of the gubernaculum exist at the beggining of fetal development and disappear during testicular migration (1, 29, 30). Pubopenile testicular ectopia is considered the rarest form of this anomaly, but in one study with fetuses, the only two cases of anomalous insertion of the gubernaculum were located in the pubopenile region (31).

Structure of the gubernaculum during testicular migration

The different parts of the gubernaculum undergo varied changes during testicular migration. The vaginal and infra-vaginal portions become proportionally longer as the testis starts to descend to the scrotum. At the same time, their diameter increases, a fact considered by Heyns (3) to be one of the most important mechanisms for dilating the inguinal canal to allow the testis to pass.

The gubernaculum's growth is divided into two phases, triggered by different hormonal stimuli (12, 18). In the first, its volume increases and in the second it decreases in size, coinciding with the complete descent of the testis (32). The cremaster muscle presents structural alterations during this period as well (33). This muscle allows rhythmic contraction to guide the testis into the scro-

tum in rats and in humans, leading to eversion of the distal portion of the gubernaculum and contributing to its migration to the scrotum (33).

The first phase is characterized by pronounced cell multiplication and accumulation of glycosaminoglycans, mainly hyaluronic acid. These substances act as hydrophilic agents and raise the quantity of water. There is also an increase in the amount of extracellular material, explaining the low cell density found at some points (34, 35). The presence of myoblasts intensifies and there are changes in the number and arrangement of the collagen fibers and alterations of the elastic system.

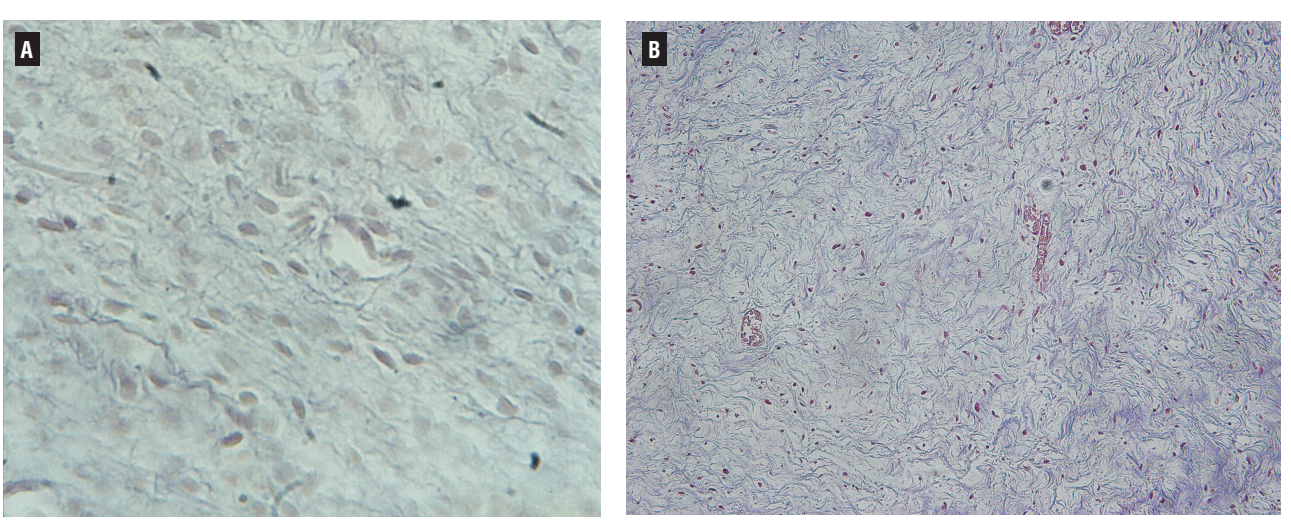
In the second phase, the gubernaculum shrinks, particularly its length, normally accompanied by descent of the testis. This phenomenon appears to be androgen-dependent and brings substantial degradation of the glycosaminoglycans previously accumulated in the extracellular material, with consequent dehydration of this space and condensation of the gubernaculum (22). Although no estimates are available of the degree of shortening, some authors believe this occurs along with other factors, causing the gubernaculum to convey the testis to the scrotum (3, 18).

Understanding the relationship between regression of the gubernaculum and descent of the testis is vital to comprehension of how androgens control testicular migration. Studies have demonstrated an association between androgen deficiency, on the one hand, and failed regression of the gubernaculum and cryptorchidism on the other. In this situation, the gubernaculum appears to act as an obstacle to testicular descent (36, 37).

Differences between the proximal and distal portions of the gubernaculum have been reported. In one study, in fetuses aged 15 to 35 WPC the authors observed a greater number of muscle cells in the distal portion, arranged in isolated groups, while in the proximal portion the muscle tissue was present in smaller quantity and was arranged peripherally. With increasing age, the quantity of muscle tissue was found to decrease. In fetuses between 28 and 29 WPC, the authors observed a large quantity of elastic fibers and almost no muscle fibers in the entire gubernaculum (22).

In the early fetal period (15 and 16 WPC), when the testes are still in the abdomen, the connective tissue is loose and poor in collagen (Figure-2A). As the gestational time increases and the testes migrate from the abdominal cavity, the connective tissue becomes progressively denser and richer in collagen (Figure-2B). In fetuses with 28 to 29 WPC, the gubernaculum presents very dense organization of the

Figure 2 - A) Photomicrograph of a male fetus with 15 weeks post-conception with both testes situated in the abdomen. A low concentration of collagen and elastic fibers in the gubernaculum can be observed (HE, 400x). B) Photomicrograph of a male fetus with 35 weeks post-conception with both testes situated in the scrotum. A condensation of the gubernaculum with a large amount of collagen and elastic fibers can be observed. Masson's trichrome, 200x.



collagen fibers and predominance of fibroblasts, with sharp directional orientation of the fibers and cells (22). Likewise, the reticular fibers, which are arranged more loosely in the gubernaculum at the beggining of the fetal period (15 and 16 WPC) are very dense in the gubernacula of fetuses with 28 and 29 WPC (22).

Changes in the tissue components of the gubernaculum during the fetal period have been reported in various experimental studies (34, 35). The relative presence of muscle tissue appears to be one of the factors that affect the traction the gubernaculum exerts on the testis during its migration (1, 3, 6). At the beggining of the fetal period, a good deal of muscle tissue is present, but it starts to diminish with time, while the elastic tissue, which is sparse at the start, is markedly higher when the fetus reaches 25 WPC. At 28 and 29 WPC, under normal circumstances the testes have already completed their migration and are located in the scrotum. At this point of gestational age, Costa (22) observed very sparse muscle fibers and a large quantity of elastic fibers in the gubernaculum, especially in the distal portion.

The connective tissue of the gubernaculum undergoes remodeling, so that at the end of migration it has essentially become a fibrous structure, rich in collagen and elastic tissue (22). The tissue changes in the gubernaculum testis during the fetal period suggest that it plays an active role in testicular migration.

In summary, the morphological alterations of the extracellular matrix of the gubernaculum likely lead to a reduction of its length and volume. Although there is not sufficient evidence to estimate the degree of shortening, this change probably acts synergistically with other factors, causing the gubernaculum to guide the testis to the scrotum (22). Testicular descent is therefore a complex and multifactor event, and cryptorchidism should be viewed as a disease with multiple etiologies.

One of the factors involved in cryptorchidism is the failure of the gubernaculum to migrate all the way to the scrotum (38). Structural studies conducted in patients with cryptorchidism reveal significant changes in the gubernaculum's structure, with a higher quantity of fibrous tissue and lower concentration of collagen than in the fetal gubernaculum (39). The influence of fetal androgens on the fetal gubernaculum's development is very important for the alterations of this structure, and the changes in its secretions can be one of the factors involved in cryptorchidism (40). For example, in a study analyzing the structure of the gubernaculum in patients treated with hCG, the authors observed that the gubernacular components change significantly when submitted to hormonal treatment, with an increase in the concentration of elastic and striated muscle fibers and a decrease in the volumetric density of collagen (41).

CONCLUSIONS

In the first phase of testicular migration, the gubernaculum enlarges to hold the testis near the groin and in the second phase the gubernaculum migrates across the pubic region to reach the scrotum.

The proximal portion of the gubernaculum is attached to the testis and epididymis and the presence of multiple insertions in the distal gubernaculum is extremely rare.

The presence of muscles and nerves in the human gubernaculum is very poor.

The gubernaculum presents significant structural modifications during testicular migration in human fetuses.

The gubernaculum of patients with cryptorchidism has more fibrous tissue and less collagen, and when patients are submitted to hormonal treatment, the gubernacular components change significantly.

ACKNOWLEDGMENTS

Supported by grants of CNPQ and FAPERJ.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 730-737, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.03

Brazilian Abstracts Presented at the American Urological Association Annual Meetings: Contribution, Publication Rates, and Comparison with Oncology Abstracts

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ABSTRACT

Purpose: Scientific research originating from Brazil appears to be rising in several medical fields. Research results are often presented at scientific meetings before publication in peer-reviewed journals. We investigated the publication rate of Brazilian studies presented in American Urological Association (AUA) meetings and compared with the rate of publication of Brazilian oncological studies presented at the American Society of Clinical Oncology (ASCO) meetings.

Materials and Methods: a hand search of 12,454 abstracts presented at aua meetings 2001-2007 was conducted. abstracts for which at least two-thirds of institutions were from brazil were considered as brazilian. final publication was searched in pubmed and lilacs databases. oncological abstracts were also hand searched in the asco meetings proceedings in the same years.

Results: There was no significant temporal trend in the proportion of AUA studies originating from Brazil along those 7 years. A total of 195 abstracts (1.57%) were from Brazil. One hundred (51.3%) abstracts were published in full, and the estimated 5-year publication rate was 48.2%. There was a progressive increase in publication rates for studies categorized as video, poster, and podium presentations. Considering abstracts presented in years 2001-2005, urologic publication rate was significantly higher than for abstracts presented at the ASCO meeting.

Conclusions: Our results suggest that the Brazilian contribution to AUA meetings is at a plateau and that the Brazilian literature contribution is greater in urology than in oncology. Efforts must be invested towards raising this plateau and understanding qualitative aspects of the urology scientific output from Brazil.

ARTICLE INFO

Key words:
Bibliometrics; Brazil; meeting abstracts; neoplasms; research design; urology

Int Braz J Urol. 2014; 40: 730-7

Submitted for publication:
December 05, 2013

Accepted after revision:
May 03, 2014

INTRODUCTION

The presentation of abstracts at scientific meetings, often before attempts at publication in peer-reviewed journals, is an integral component of medical research. However, many studies presented in abstract form are never published in full (1,2). The American Urological Association (AUA) Annual Meeting is considered the premier source from which urology professionals from all over the world can learn about the latest advances in this field (3). Previous authors have investigated

the fate of abstracts presented at the AUA Annual Meetings (4-8). Likewise, work has been done to assess the fate of Brazilian studies presented as abstracts in the 2003 meeting of the Brazilian Society of Urology (9). To our knowledge, however, there have been no previous studies on Brazilian abstracts presented at AUA Annual Meetings. We and others have shown an increasing Brazilian contribution in the areas of cardiology, neurology, oncology, and psychiatry, among others (10-13). In the current study, we attempted to quantify the scientific output from Brazil in recent editions of the AUA Meetings. As a secondary goal, we aimed to compare the urological scientific output with the experience described previously in oncology, which has shown that the Brazilian contribution in this field is quantitatively increasing in a statistically significant fashion, albeit with low publication rates (13).

MATERIALS AND METHODS

Selection of abstracts

The selection of abstracts was done following the same method used in a prior study in oncology, in which Brazilian abstracts accepted for the Annual Meetings of the American Society of Clinical Oncology (ASCO) were analyzed (13). Briefly, a hand search of the Program Proceedings of the AUA Annual Meetings for the years 2001 through 2007 was conducted. Studies accepted by the program committee of the AUA Annual Meetings may be presented in several forms, including podium (oral), poster, and video presentations. Despite the fact that poster presentations received varying denominations along the years comprised in the study period, all such denominations were grouped under the same category for the current analysis. During the search, an attempt was made to identify all Brazilian studies, which were defined as those for which at least two-thirds of institutions were from Brazil (i.e., multinational studies which included Brazilian investigators were not analyzed unless the aforementioned criterion was met). Studies described in the abstracts were categorized, on the basis of their profile, as predominantly basic-science, clinical, or epidemiological research. Importantly, no attempt was made to appraise the results or scientific merit of the studies.

Search for full papers

For each abstract included in the analysis, PubMed and Lilacs databases were used with the goal of locating its full publication. The search strategy consisted of using the last names of the first or last authors for each abstract, in addition to one or more keywords related to the subject of interest (13,14). Date of publication was the date of the journal issue, when available, or the 15th day of the month of publication otherwise. For full publications that originated from abstracts presented in more than one AUA Meeting, only the abstract first presented was considered as published, whereas subsequent AUA presentations of the same study were considered as non-published.

Statistical analysis

Proportions were calculated, with corresponding 95% confidence intervals (CI) when appropriate. The variation in the proportion of Brazilian studies along the years was assessed using the chi-square test for trend. The time to full publication of the abstracts was estimated using the Kaplan-Meier method. Although we had publication data for urology abstracts for the whole study period (2001 through 2007), a comparison was undertaken between the publication rates of the urology abstracts for years 2001 through 2005 and the oncology abstracts for these same years described elsewhere, since we had no data for oncology abstracts for the years 2006 and 2007 (13). However, the search for full publications of the oncology abstracts was updated for the present study, in order to provide the same median follow-up times—as measured from each annual meeting analyzed—for both specialties (these two annual meetings usually take place only one month apart). The curves of time to publication were compared between types of urology abstract, as well as between urology and oncology abstracts, using the log rank test. All reported P

values are two-sided, and statistical significance was considered if P<0.05. The software used was MedCalc (Mariakerke, Belgium).

RESULTS

Number and features of Brazilian studies

A total of 12,454 abstracts published in the AUA Program Proceedings were screened. Of this total, 195 were Brazilian studies, for an annual average of 27.9±9.3 abstracts. Therefore, Brazilian studies represented 1.57% of all studies presented at the AUA Meetings analyzed (95% CI, 1.36%–1.80%). Among the 195 Brazilian studies, 163 (83.6%) were categorized as clinical investigation, 25 (12.8%) as basic research, and seven (3.6%) as epidemiologic research. Brazilian states with the highest number of abstracts from a single state were São Paulo (N=148), Rio de Janeiro (N=21) and Rio Grande do Sul (N=16); the remaining 10 abstracts were from other states (N=5) or from more than one state. No support from financial sources were declared in 189 abstracts; for the remaining six, pharmaceutical industry was declared as a source of support in three studies, and government or private grants were acknowledged in three cases.

Temporal trends in Brazilian urology studies

Figure-1 displays the number of Brazilian studies accepted by the program committee of the AUA Meeting between 2001 and 2007. There was no significant trend in the proportion of Brazilian studies along the 7 years comprised in the study period, in relation to the overall number of abstracts accepted each year (P=0.743).

Publication of urology abstracts

The publication rate of urology abstracts for the period 2001 through 2007 is shown in Figure-2. Four studies giving rise to full publications were presented in more than one AUA Meeting (thus, only the first abstract was considered as published in each of these four cases). Of 195 abstracts analyzed, 100 (51.3%; 95% CI, 44.1% to 58.5%) were published in full. The Kaplan-Meier estimate for publication rate at 5

Figure 1 - Absolute numbers (shown inside the graph) and percentages (Y-axis) of Brazilian studies presented at the American Urological Association in years 2001 through 2007 (P for trend=0.743).

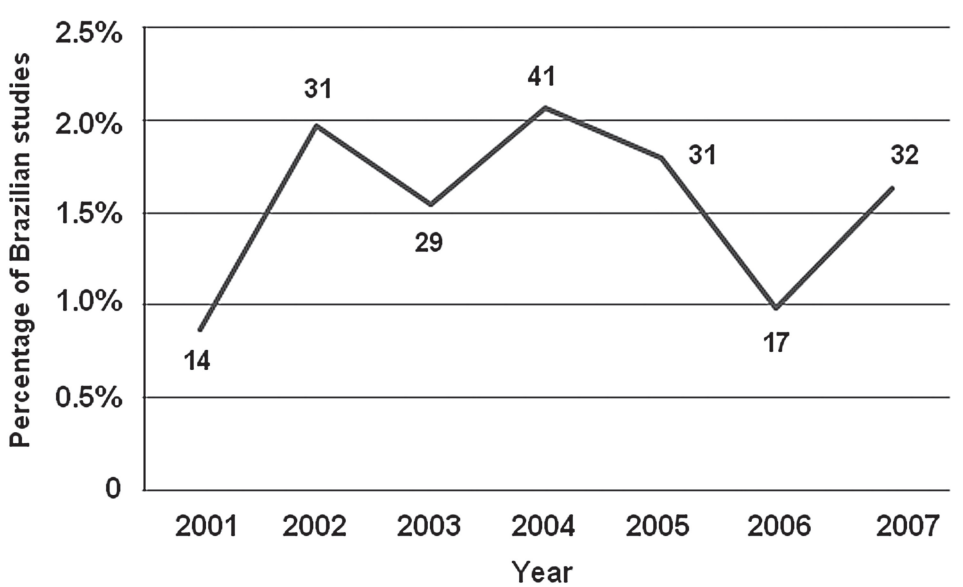
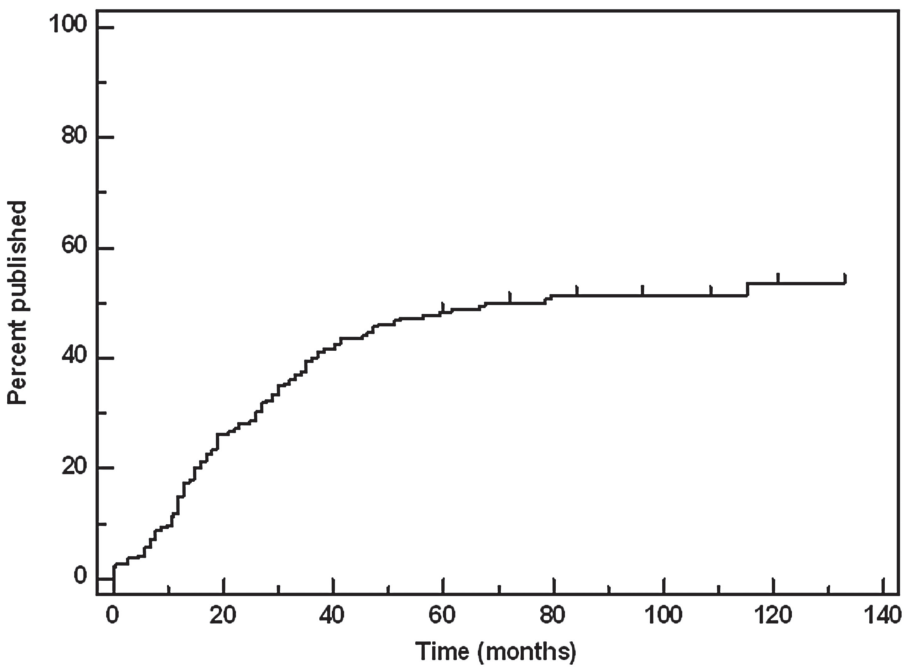


Figure 2 - Time to full publication of Brazilian studies presented at the American Urological Association Annual Meetings between 2001 and 2007 (tick marks represent censoring).



years was 48.2%. Four abstracts were published in full before the date of the corresponding AUA Meeting (with a range of 2.5 to 7.6 months); for these papers, we considered the time to publication as zero, in order to avoid negative times. When only published papers were considered, the median time to publication was 18.8 months. Of the 100 published studies, 55 appeared in print within 2 years from presentation of the abstract. The publication rates for each of the 7 year comprised in the study period were 50%, 51.6%, 41.4%, 56.1%, 41.9%, 52.9%, and 46.9%, respectively (P for trend=0.840). As shown in Figure-3, there were statistically significant differences in publication rates among urologic studies categorized as podium, poster and video presentations (P=0.006 for the comparison among the three categories).

Comparison between urology and oncology abstracts

In comparison with the rate of contribution from Brazil in the field of oncology (i.e., to the ASCO Meetings 2001 through 2007), there was a significantly higher rate of Brazilian contribution to the AUA Meetings 2001 through 2007 (Table-1). With regard to publication rates, Figure-4 shows that the 146 urology abstracts (2001 through 2005) were more likely than the 154 oncology abstracts (2001 through 2005) to be published in full. The hazard ratio for this comparison is 1.51 (95% CI, 1.07 to 2.12), indicating that urology abstracts have a nearly 50% higher chance of being published (P=0.019).

DISCUSSION

The current analysis suggests that the Brazilian scientific output in urology is at a plateau in relation to the AUA Meeting. On the other hand, the study also suggests that the publication rate of such studies in indexed journals is not trivial, and that the urology contribution is higher than that of oncology. Our results may be put in perspective by comparing them with those from similar assessments conducted in urology and in other fields. Oliveira et al. found that 39% of the abstracts presented in oral fashion at the

Figure 3 - Time to full publication of Brazilian studies, according to category of presentation at the American Urological Association Annual Meetings 2001 through 2007 (tick marks represent censoring).

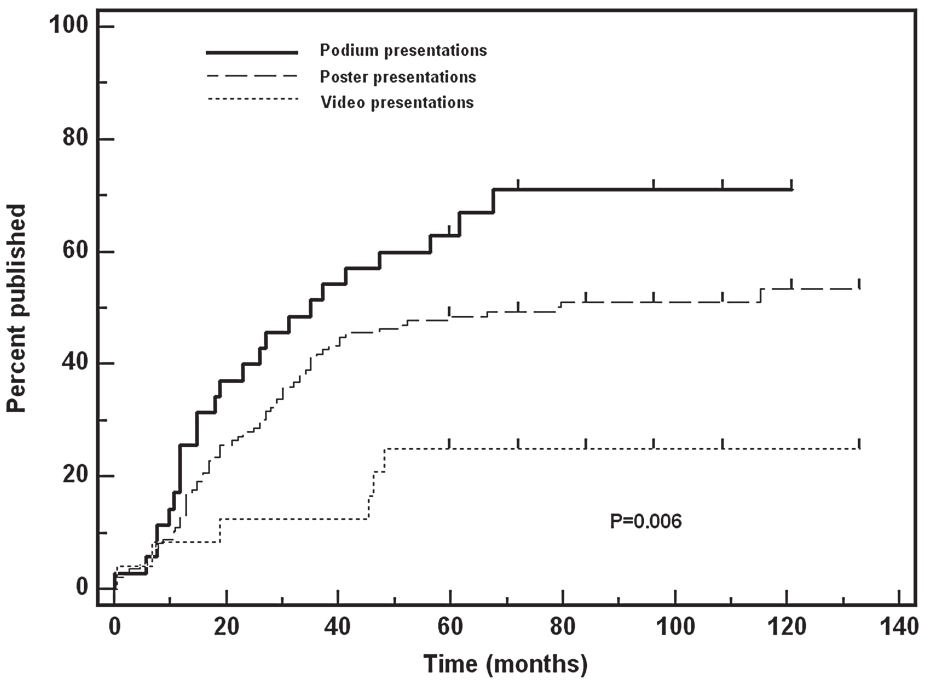
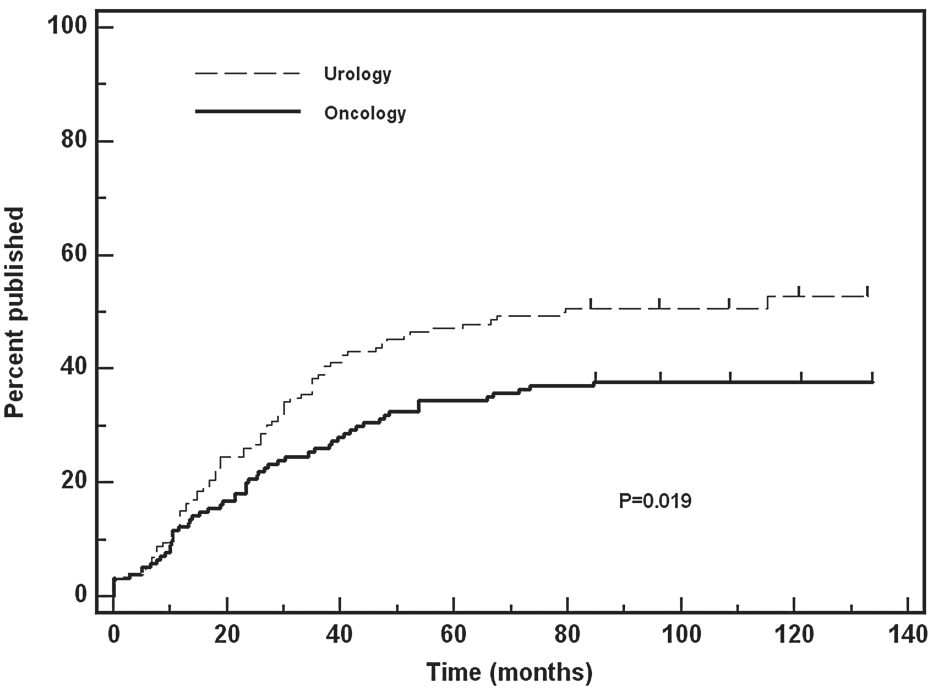


Table 1 - Comparison of contribution rates from Brazilian studies presented at the American Urological Association and American Society of Clinical Oncology Annual Meetings 2001 through 2007 (data for oncology are from Pinheiro et al.[22]).

Annual Meeting	Proportion of Brazilian Abstracts	P value
American Urological Association	1.57% (195 of 12,454)	<0.001
American Society of Clinical Oncology	0.97% (244 of 24,998)	

Brazilian Society of Urology meeting 2003 were published (9). Regardless of presentation type, overall publication rates ranging from 37.8% to 55% were reported in studies that assessed AUA Meetings, (4,5,8) whereas Fesperman et al. found a rate of 33.5% when the Southeastern Section of AUA was considered (6). Likewise, Autorino et al. reported a publication rate of 47.3% for abstracts presented at the European Association of Urology Meetings 2000-2001 (15), whereas Rao et al. found a rate of 42% for abstracts presented at the annual meetings of the British Association of Urological Surgeons (16). On the other hand, a rate of only 29.8% was found for abstracts presented at annual meetings of the Urological Society of Australia and New Zealand (17). The fate of abstracts presented at scientific meetings has been analyzed in several other fields. In a landmark study, Goldman and Loscalzo described the fate of cardiology abstracts presented at three meetings, and found that 49.6% of them were published in peer-reviewed journals (18). In another study evaluating abstracts presented at the ASCO Meeting, De Bellefeuille et al. found that 58% of abstracts led to full papers (14). Publication rates have also been reported in radiology (35%) (19),

Figure 4 - Time to full publication of Brazilian studies presented the American Urological Association and American Society of Clinical Oncology Annual Meetings 2001 through 2005 (data for oncology were updated from Saad et al. [13]; tick marks represent censoring).



in orthopedics (34%) (20), and in plastic surgery (45%) (21), among other fields. A meta-analysis of 79 reports that examined the publication rates of studies initially presented as abstracts showed that 44.5% of these studies get published (2). Thus, the publication rate found for Brazilian urology abstracts in our study is on the high end of publication rates reported worldwide and in different medical fields. Of note, the graded increase in publication rates according to type of presentation observed in the current study was also noted by Hoag et al. (8), but not by Rao et al. (16). Podium presentations are more prone to be published, probably reflecting a better quality of such studies.

The fact that our methodology was used previously in oncology (13) allowed for a comparison between these two areas in the same period of time (2001-2005), showing that urology abstracts are more prone to be published (51.4%) than oncology abstracts (37.7%). Although we believe this comparison between the output of urology researchers and oncology researchers from Brazil is adequate, as it involves the same years and meetings of equivalent magnitude within their corresponding fields, we should point out that this is an univariate comparison, as we could not adjust for confounders, such as type of presentation and type of the research. With regard to the former, the differences between the two meetings preclude proper adjustment; as for the latter, we did not appraise the contents of abstracts or its quality. It is possible that these or other important determinants of publication rates differ between the groups compared.

In addition to the comparison of publication rates, our study allows for the comparison between urology and oncology in terms of their relative contribution to their corresponding scientific meetings (Table-1). Although the period analyzed was relatively short, the data suggest that the contribution rates in urology fluctuated around an annual stable average, whereas for oncology there was an upward trend (13,22).

We may speculate that the stability of contribution rates in urology is a sign of greater scientific maturity of this specialty in Brazil, with opposing interpretation in the case of oncology, a newer specialty. On the other hand, such scientific maturity hovers around a plateau that may or may not be considered as adequate in terms of what Brazilian urology researchers would like to see for their specialty. Unfortunately, we have not been able to quantify the contribution of other countries to AUA Meetings, as done by our group in the case of oncology (23). It is important to stress out the reasons why we searched the AUA Meetings from 2001 through 2007; such years were chosen with the aim of allowing a relatively long follow-up since the original presentation of abstracts. This action prevented that time would be a limitation for the abstracts to be written and published.

We believe this type of study is important for the Brazilian scientific community, as it allows for a quantitative assessment of the relative contribution from Brazilian investigators to the international scenario. However, our study has some limitations. First, we only looked at studies presented at the AUA Meeting. Although considered by many as the most important scientific event in urology, this meeting is one of many international events at which Brazilian investigators might present the results of their studies. Thus, it is possible that the analysis of other meetings would show different rates of Brazilian investigators' contribution. A second limitation stems from the fact that we assessed the proportional Brazilian contribution in the form of abstracts. It is conceivable that good-quality Brazilian research during the 7 years analyzed was submitted for full publication without prior presentation at the AUA Meeting. Such possibility would lead to an underestimation of the Brazilian productivity, as long as researchers from the rest of the world behaved in a different manner, i.e., had a higher trend than Brazilian investigators to present their results as abstracts before attempting full publication. A third limitation of this type of analysis is that it does not allow for an assessment of a differential rate of acceptance of Brazilian studies by the program committee of the AUA Meeting, in comparison with studies from the rest of the world. Since the total number of studies per country submitted to the meeting (i.e., the denominator of the proportion of accepted studies per country) is not known, this comparison cannot be made. A fourth limitation of our study is that we only assessed quantitative aspects of the abstracts, as their quality was not directly analyzed. We believe this type of analysis would be a bit less informative, as far as determining the contribution of Brazilian studies to the worldwide literature. In addition, we only analyzed the AUA meeting and no national meetings. Finally, some of the abstracts could be published in years that we did not evaluate, which could increase the publication rate of both groups.

CONCLUSIONS

Our study suggests that the Brazilian contribution to AUA Meetings is at a plateau. Future studies could be done in order to better understand qualitative aspects of the urology scientific output from Brazil, as well as quantitative aspects related to the published literature. Finally, our study suggests that the Brazilian contribution to the international literature is greater in urology than in oncology, both in terms of percentage of abstracts in equivalent scientific meetings and in terms of indexed publications.

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ORIGINAL ARTICLE

Vol. 40 (6): 738-744, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.04

Epidemiological study of penile cancer in Pernambuco: experience of two reference centers

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ABSTRACT

Objectives: To investigate and analyze the epidemiological profile of penile cancer in the state of Pernambuco and compare this information with other studies related to the issue.

Material and Methods: We conducted a retrospective, observational and descriptive study of all patients with penile cancer in two reference centers in Pernambuco - Brazil, from 2007 to 2012. The variables studied were: age, region from the state, socio-economic situation, previous postectomy, smoking, time from the beginning of injury to diagnosis, staging of the primary lesion, tumor differentiation, treatment performed and death due to cancer.

Results: The total number of patients was 88. The highest prevalence was seen in those aged between 66 and 75 years. About the socio-economic situation, 67% worked informally and 64.8% received up to two minimum wages. Of all patients, 57% were married and 50% illiterate. The Metropolitan Region of Recife was the one with the highest number of cases, 41%. Tobacco smoking was reported in 48.9% of cases and prior postectomy in 3.4%. Most often it was observed an average period of six months from the onset of symptoms to diagnosis. And when the lesion was diagnosed, it usually had 2 to 5 cm (64.7%), stage T2 in 50% and well differentiated in 79.6%. Partial penectomy was performed in 76.1% and total in 17%. Death was observed in 27.3%.

Conclusion: The clinical profile and epidemiological characteristics found in this study are similar to other national and international studies related to the issue, i.e., typical of underdeveloped or developing countries.

ARTICLE INFO

Key words:
penile cancer; epidemiology

Int Braz J Urol. 2014; 40: 738-44

Submitted for publication:
January 12, 2014

Accepted after revision:
May 05 2014

INTRODUCTION

Penile cancer (PC) is a rare observed tumor in developed countries in North America and Europe. In the USA, the incidence is 0.2/100,000 inhabitants (1); in Spain, the incidence is between 0.7 and 1.5/100,000 (2).

However, in many countries of Africa, South America and Asia, the disease represents an important health issue. Most cases in the world occur in India, Brazil and Uganda, with an incidence four (3) to six (1) times higher than the above developed countries.

In Brazil, the highest incidences occur in North and Northeast regions, where most penile amputations are performed (4). However, there are very few epidemiological studies in the country in order to categorize that affected population.

The main objective of the present work is to evaluate the epidemiological and clinical

characteristics of penile cancer in the state of Pernambuco (Brazil) in order to gather information about the disease in this region and to compare these data with other published in literature.

MATERIALS AND METHODS

This is a retrospective, observational, descriptive study, performed in the first semester of 2013. The data of the medical records of PC patients from Hospital do Cancer de Pernambuco (HCP) and Hospital Getulio Vargas (HGV) were reviewed. These are reference centers for this disease in the state. The reviewed data were from patients attended from January 2007 to December 2012. These hospitals are located in the city of Recife, capital of the Pernambuco State, situated in the Northeastern region of Brazil. Four patients were excluded: two from the state of Paraiba and two from the state of Alagoas.

The studied variables included: age, region of the state, marital status, work status, degree of education, socio-economic status, previous postectomy, smoking, period from the beginning of lesion until diagnosis, staging of primary lesion (TNM 2010), tumor differentiation, treatment performed, presence and localization of tumor recurrence, treatment of tumor recurrence and death due to PC.

The research was approved by the Ethical Committee of Federal University of Pernambuco.

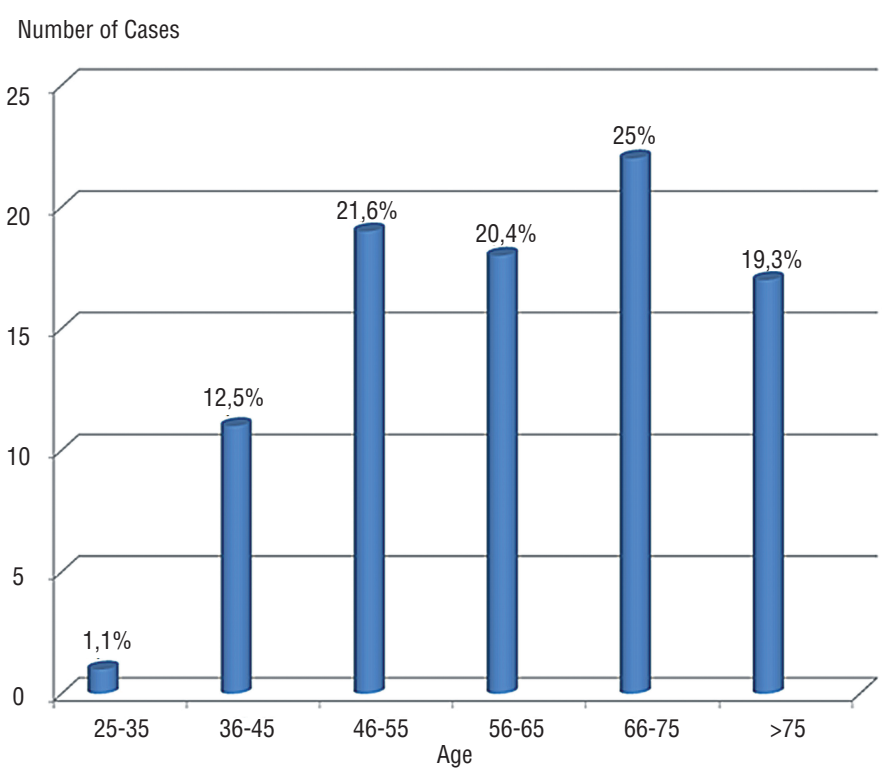
RESULTS

Eighty-eight charts were reviewed, 76 from HCP and 12 from HGC. In 2010, according to the Brazilian Institute of Geography and Statistics, male population of Pernambuco state was 4,229,897, and penile cancer incidence was 2.08/100,000. Median age of patients was 61.2 years (±12.57) and the highest prevalence was observed in those with 66 to 75 years (25% of total) (Figure-1).

In relation to marital status, 57% were married, 33% single and 10% Widower.

Most had an informal job (67%), 25% had a formal work and 8% were unemployed. 23.8% had an income of less than a minimum wage (MW), 64.8% one to two MW and 11.4% three to four.

Figure 1 - Geographic distribution of penile cancer in Pernambuco.



Fifty percent of patients were illiterate, 43.2% studied only until first grade and 6.8% attended high school.

Figure-2 shows that the metropolitan region of Recife was the region of the state that presented most cases. 48.9% of patients smoked and 3.7% were submitted to a previous postectomy.

In 68.1% of charts there was no information about the period between the initial symptoms and diagnosis. Among those with these data, 39.2% were diagnosed by biopsy of penile lesion that was performed up to six months from the beginning of symptoms, 25% after 7 to 11 months and 35.7% after one or more years.

Tumor size at diagnosis was less than 2 cm in 11 patients (12.5%), 2-5 cm in 57 patients (64.8%) and more than 2 cm in 20 patients (22.7%). Most patients presented T1 or T2 stages (36.4% and 50%, respectively – Table-1); 68.1% were N0 and 31.9% had positive lymph nodes. No distant metastasis was observed. 79.6% of lesions were well differentiated, 13.6% moderately differentiated, 5.7% undifferentiated and 1.1% sarcomatoid.

Surgical treatment is presented in Table-2. Adjuvant chemotherapy (AC) was performed in three cases. Four patients received palliative radiotherapy (RT). CT and RT were associated in two patients.

Six patients received only clinical treatment (terminal patients).

PC relapsed in 28 patients (31.8%), 56% locally and 46.4% inguinal. Recurred lesions were treated according to Table-3.

Death occurred in 24 patients (27.3%) but it was not possible to stablish cancer-related death by other causes.

DISCUSSION

PC is the fourth most common tumor in men, after prostate, bladder and kidney cancers; it represents 2% of all malignant tumors of men, and caused 363 deaths in 2010 in Brazil (5).

Frequency is variable, according to the analyzed region. In Brazil, the most frequently mentioned paper about PC epidemiology is the Brumini's et al. work (4), that states that the higher

Figure 2 - Number of cases of penile cancer according to age.

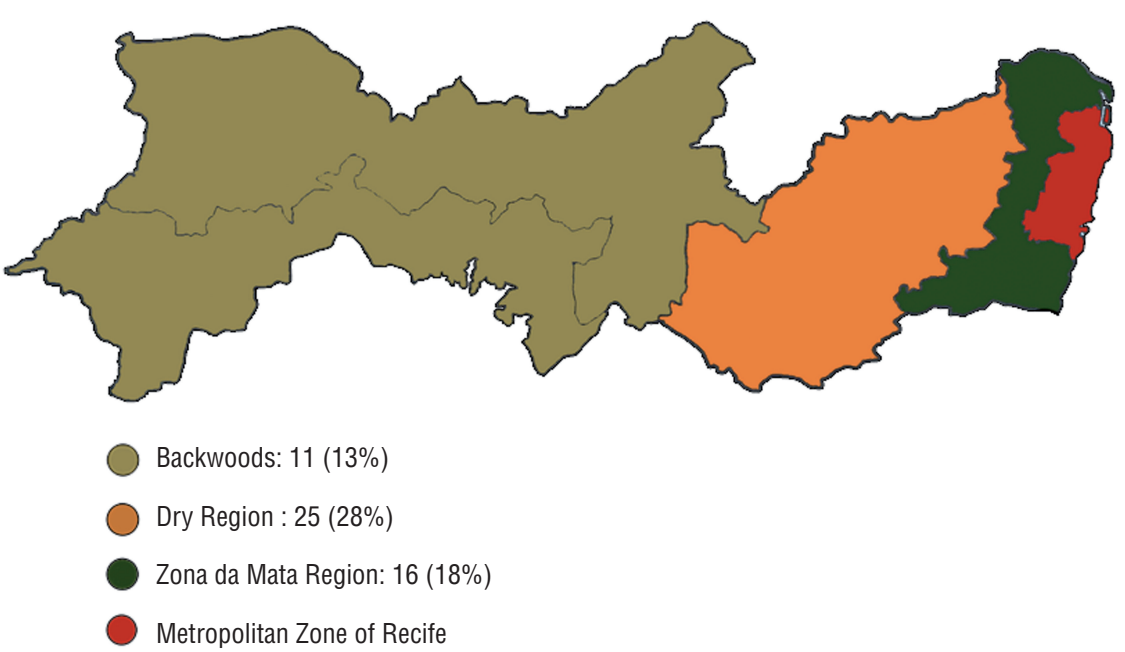


Table 1 - Staging of penile cancer patients.

Staging*	Number of Cases (%)
Tis	Zero
Ta	Zero
T1	32 (36.4 %)
T2	44 (50 %)
T3	7 (7.9 %)
T4	5 (5.7 %)
Total	88 (100 %)

* Classification TNM da American Joint Committee on Cancer, 2009.

Table 2 - Treatment.

	No. Patients Treated (%)
Partial penectomy	67 (76.1%)
Total penectomy	15 (17%)
Unilateral lymph node dissection	3 (3.4%)
Bilateral lymph node dissection	14 (15.1%)
No lymph node dissection	65 (73.9%)

Table 3 - Treatment after tumoral recurrence.

Surgery	No. Patients Treated (%)
Surgery + Chemotherapy (CT)	6 (21.4%)
Surgery + Radiotherapy (RT)	7 (25%)
Surgery + CT + RT	3 (10.7%)
CT + RT	3 (10.7%)
CT	1 (3.5%)
RT	1 (3.5%)
No treatment	1 (3.5%)

incidence is observed in the northeast (5.7%) and north regions (5.3%). But this is a study performed in 1982 with data from 1976 to 1980. Favorito et al. (6) related a higher description of cases in the Southeast region (45.54%), in particular in the state of São Paulo. This fact can be explained due to the higher economic power of that state, to where most cases migrate in order to search for treatment, in particular from the north and northeast regions.

This same dynamics is observed in the state of Pernambuco, where it was observed the highest incidence of PC in the metropolitan area of Recife. The higher economic status of the capital attracts several people from other regions, in search for work and better living conditions with better medical care, allowing for more precise diagnosis and treatments. The same aspects are observed in studies performed in the metropolitan regions of Salvador, capital of Bahia state (7), and Belem, capital of Pará state (8).

The incidence of PC in the Pará study was 5.7/100,000 inhabitants (8), higher than the present series, 2.08/100.000 inhabitants. But this figure is underestimated, since there are others hospitals than these two reference centers in the region with more cases. Even so, the incidence is higher than that of Jews (9), North Americans (9) and Europeans (2).

The higher prevalence of the disease was observed in the sixth and seventh decades of life, similar to other national studies (6,8) and the world (2,10,11). It was also observed a significant amount of PC cases in young adults, with less than 45 years old (13.6%), what was worrying, since mutilation was performed in fully sexual active men.

Frisch et al. (12) described three risk factors for the development of PC: phimosis/long foreskin, low social economic status and bad local hygiene. These factors are coincident with our results: most patients had an informal job (67%), with income lower than two minimum wages and many were illiterates (50%). Most studied patients had a bad cultural status, with compromised personal hygiene, with high risk sexual behavior (unprotected sexual relations, promiscuity) and exposition to sexually transmitted diseases (HPV) that

could be related to PC (13). It is also important to stress the habitus of zoophilia, common in interior regions of the country, increasing the chance of PC occurrence, as related by Zequi et al. (14). This aspect was not analyzed in our series since it was not possible to obtain this information in the reviewed charts.

Phimosis/long foreskin, mentioned by Frisch (12), could be present in 96.6% of patients, since only 3.4% had been previously submitted to postectomy. These features could lead to smegma accumulation and chronical inflammation, precursor to PC (15). Circumcision, as observed in Jews, has a preventive role, when performed after birth (16); Maden et al. (17) stated the incidence of PC is also lower when circumcision is performed in older children or adolescents, and in a recent study by Larke et al. (18) it was proved that when circumcision is performed until 18 years of age it also protects against invasive PC.

Dodge et al. (19) compared Uganda and Kenya, neighbor countries located in Eastern Africa, with similar geopolitical and socio-cultural aspects. But the Kenyans usually submit (due to cultural and religious causes) their adolescents to circumcision, in a ritual of passage from childhood to adult life; only the minority muslin Ugandans are routinely circumcised. The procedure affects directly the incidence of PC in these countries; in Kenya, the incidence is 1.9% of all neoplasms and 7.15% in Uganda, being in this country the most common cancer in men.

On the other hand, in Scandinavia it is not culturally usual to perform circumcision and even so, the incidence of PC is very low, probably to good cultural status and personal hygiene, including the low income population (12). According to this, it is possible to wonder which would be the most efficient method of prevention for our population: better hygiene awareness or routine circumcision for high risk groups. It is important to stress the presence of surgical complication after circumcision and the benefits and risks, and these measures should be studied by health care providers.

Among all studied patients, 58% were married and 51% of these had PC at T1 phase, in accordance to Rippentrop et al. (20), that stated that married men presented with more precocious disease, probably due to spouse stimulus to seek for health care.

60.7% of patients waited more than 7 months to be diagnosed with PC, in accordance to the Kenyan study (21), where more than 80% of patients were diagnosed after 6 months of symptoms, and to the Belem study (8), where the patients waited for up to 11 months until diagnosis. This fact can be explained by ignorance, taboos, bad health care system, inappropriate treatments by uninformed physicians, delay to referral to urologists; these aspects are associated with late diagnosis and more advanced disease.

There was no significant relation between PC and smoking, as related by Harish et al (22); in our studied populations, smokers and non-smokers were equally present.

It was also observed that 63.6% of patients presented with more advanced disease (≥ T2) and 87.5% with lesion > 2 cm. These results are similar to a Brazilian epidemiological study of PC (6), in a study performed in the state of Pará (8) and in the Kenyan study (21). And different from the North American study (10), where 62.4% of patients were diagnosed in the initial and localized phases. The bigger the lesion and the more invasive, the higher is the possibility of lymph node involvement and worse prognosis (23).

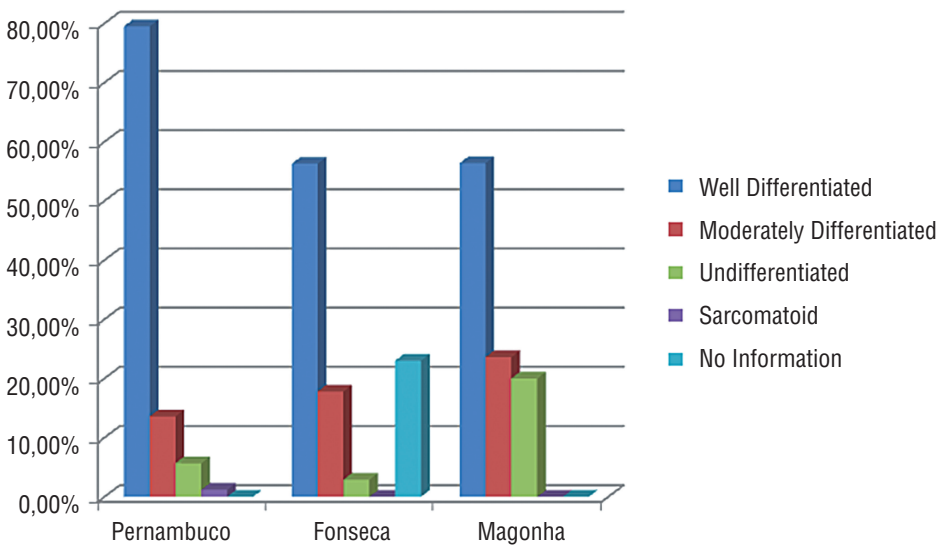
Tumor differentiation had the same characteristics of other papers (8,21), being well differentiated carcinoma the most common observed tumor (Figure-3).

Most patients were submitted to penile amputation in some degree, reflecting the advanced characteristic of the disease.

Adjuvant chemotherapy and palliative radiotherapy, isolated or combined, were used in nine patients. Different treatments were performed in similar clinical settings. These facts reflect the lack of standardization of the treatment of penile cancer nowadays, particularly in relation to lymph node involvement (24-27).

Another aspect is that, even in the presence of relatively easy diagnosis, many patients seek treatment in a stage beyond any possibility of treatment, representing 7% of our series. This fact is in accordance to the Kenyan study (20) (9%) in

Figure 3 - Tumor differentiation.



2000 and to the Salvador-Bahia study (7) (7.3%) in 1984, probably due to the same previously described factors: ignorance, low cultural status, taboos, bad hygiene, etc.

Death occurred in 24 studied patients, but it was not possible to determine the cause of death, if due to PC. Probably this figure is underestimated since many patients lost follow-up and do not report death due to this neoplasm. Mutilation and death related to penile cancer are frequent, affecting self-esteem, causing psychological damage to the patients and to their families.

It is important that health care providers and politicians be aware of this disease, performing campaigns for orientation about this tumor, since it is not a very well-known disease by general population. It is important to stress the need of good hygiene practices, circumcision counseling and to provide good health care access. HPV vaccine can be an alternative for PC prevention but more studies are necessary in order to determine its role. With these measures, there will be a reduction of public health expenses, mutilations and related deaths.

CONCLUSIONS

Epidemiological and clinical aspects of PC in this series are similar to those of other Brazilian (6,8) and international series (19,21), typical of underdeveloped or developing countries. Better prevention strategies and standardization of treatment are needed in order to reduce the incidence of PC.

ABBREVIATIONS

PC = Penile cancer
TNM = Tumor – lymph node – metastasis - American Joint Committee on Cancer, 2010.
HCP = Hospital do Câncer de Pernambuco
HGV = Hospital Getúlio Vargas
MW = minimum wage
CT = chemotherapy
RT = Radiotherapy
HPV = Human papillomavirus

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 745-752, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.05

Prostate-Specific Antigen testing in men between 40 and 70 years in Brazil: database from a check-up program

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ABSTRACT

Objectives: To evaluate the PSA in a large population of Brazilian men undergone to check up, and correlate the PSA cutoffs with prostate size and urinary symptoms.
Materials and Methods: This is a cross sectional study performed with men between 40 and 70 years undergone to check-up. All men were undergone to urological evaluation, digital rectal examination, prostate-specific antigen, and ultrasonography The exclusion criteria were men who used testosterone in the last six months, or who were using 5 alpha-reductase inhibitors.
Results: A total of 5015 men with an average age of 49.0 years completed the study. Most men were white and asymptomatic. The PSA in the three different aging groups were 0.9 ± 0.7ng/dL for men between 40 and 50; 1.2 ± 0.5ng/dL for men between 50 and 60; and 1.7 ± 1.5ng/dL for men greater than 60 years (p=0.001). A total of 192 men had PSA between 2.5 and 4ng/ml. From these men 130 were undergone to prostate biopsy. The predictive positive value of biopsy was 25% (32/130). In the same way, 100 patients had PSA >4ng/mL. From these men, 80 were undergone to prostate biopsy. In this group, the predictive positive value of biopsy was 40% (32/100). The Gleason score was 6 in 19 men (60%), 7 in 10 men (31%) and 8 in 3 men (9%).
Conclusions: The PSA level of Brazilian men undergone to check up was low. There was a positive correlation with aging, IPSS and prostate size.

ARTICLE INFO

Key words:
screening; prostate cancer; PSA; IPSS; check up; prostate size

Int Braz J Urol. 2014; 40: 745-52

Submitted for publication:
October 28, 2013

Accepted after revision:
April 06, 2014

INTRODUCTION

Prostate cancer is the second most commonly diagnosed type of cancer in the world, and the sixth leading cause of death in men worldwide. On a global level the incidence and prevalence of prostate cancer varies more than 25-fold worldwide, with highest incidence in developed countries of North America, Europe and Australia, and lower incidence rates in underdeveloped countries. These differences may occur due to the increased levels of screening and testing for prostate cancer in these developed countries (1-3).

The primary goal of prostate cancer screening is to reduce deaths due to prostate cancer, thus increasing life span. An additional important outcome of this type of screening would be a reduction in the development of symptomatic metastatic disease. Contemporary recommendations for prostate cancer screening incorporate the measurement of serum prostate-specific antigen (PSA) levels associated with other methods of detection

such as digital rectal examination and/or ultrasonography (4, 5).

With regards to screening accuracy, studies have demonstrated that a PSA cutoff of 4.0µg/L can detect many cases of prostate cancer; however, some will be missed. Using a lower cutoff level detects more cases, but at the cost of falsely labeling more men as potentially having cancer. Whether, for instance, the PSA cutoff is decreased to 2.5µg/dL, more than double the number of men aged 40 to 69 years will be labeled as a false positive (6, 7). These false positive results are associated with negative psychological effects. In addition, men who have a false positive result are more likely to have additional testing, including one or more biopsies in the year following diagnosis, as compared with those who have a negative test result. Almost one third of these biopsied patients experience pain, fever, bleeding, infection, transient urinary difficulties, and 1% even require hospitalization (8,9).

Theoretically, the early detection of prostate cancer in younger asymptomatic men could significantly reduce the mortality rates; however, in most cases those tumors will not progress or will progress so slowly that they would have remained asymptomatic during the lifetime of the patient. The term overdiagnosis is used to describe this situation. Lower PSA cutoffs and screening tests performed in younger men increase the probability of overdiagnosis (10). There is a high propensity for physicians to treat most cases of screen-detected cancer, given our current inability to distinguish indolent from aggressive tumors. Thus, many patients are being subjected to the harmful effects of prostate cancer treatment that will never become symptomatic (11,12).

The primary objective of this study was to evaluate the PSA levels in a large population of young Brazilian men submitted to a health check up program. The second objective was to correlate the different PSA cutoffs with aging, prostate size, and urinary symptoms.

MATERIAL AND METHODS

Data from the present study were collected from the check-up program performed between January and December 2011 at a private hospital in Sao Paulo, Brazil. This study was approved by local ethics committee and all patients signed out an informed consent.

During the examination, a multidisciplinary team composed of general clinicians, urologists, ophthalmologists, dermatologists, nurses, nutritionists and physiotherapists evaluated the patients.

Men between the ages of 40 and 70 years old were submitted to a urological evaluation, which consisted of a clinical history, International Prostate Symptom Score (IPSS) (13), digital rectal examination (DRE), prostate-specific antigen (PSA), urinalysis, and abdominal ultrasonography. The prostate size was measured by abdominal ultrasonography despite the limitations of this method. The digital rectal examination was performed in every patient over the age of 45 and/or over the age of 40 for those with a history of prostate cancer in their family, or whose race was African-American.

The inclusion criteria were men between 40 and 70 years old, without previous history of prostate and/or bladder cancer. The exclusion criteria were any type of bladder or prostate surgery, men who used testosterone in the last six months, or those who were using 5 alpha-reductase inhibitors.

All patients received an orientation (which was sent by email or mail postal service) two weeks before the check-up. Blood was drawn before beginning the examination. With regards to PSA testing, men were instructed to avoid sexual activity 72h before the exam. In cases where the PSA test was greater than 4.0ng/dL, the blood draw was repeated to confirm the result. The PSA dosage was carried out using an ultra-sensible PSA assay with a detection limit of 0.003ng/dL.

Statistical analysis was performed using SPSS software version 15.0 for Windows. Pearson's Chi-square test was used for comparison between non-numerical variables, while t-test and ANOVA was used for comparison between numeric variables. A p value of 0.05 was considered the cut off for statistical significance.

RESULTS

Of the total number of 5315 patients evaluated in this urological examination program from January to December 2011, 300 were excluded due to any one of the exclusion criteria lis-

ted above. Thus, a total of 5015 men with an average age of 49.0 +/- 4.0 years completed the study. Out of 5015 men, 3880 (77.3%) were white and only 90 (1.7%) were black. The overall prevalence of diabetes mellitus in our population was 3.9% (197/5015). These demographic data are presented in Table-1.

The average PSA was less than 2.5ng/mL for all age groups. Older men had higher values of PSA, prostate size and IPSS score.Table-2 presents the averages of PSA, IPSS and prostate size of the 5015 men.

Further analysis was performed in order to correlate different PSA cutoffs with aging, IPSS, and prostate size. The first cutoff was 2.5ng/mL. Out of 5015 men included in this study, 4723 (94.17%) had PSA less than 2.5ng/mL, 192 (3.8%) had PSA between 2.5 and 4.0ng/mL, and 100 (1.9%) had PSA greater than 4.0ng/mL. The prevalence of PSA > 2.5ng/mL was higher in older men. Higher PSA levels correlated with higher IPSS and larger prostate size. These data are presented in Table-3.

A total of 192 men had PSA between 2.5 and 4ng/mL. Among these men 130 were submitted to prostate biopsy. The predictive positive value of prostate biopsy was 25% (32/130).

Table 1 - Demographic data of 5015 men.

	40 - 49 years	50 - 59 years	60 - 70 years	p
N	2813 (56%)	1726 (34.5%)	476 (9.5%)	0.001
Race				
White	2700 (95.1%)	1650 (95.5%)	430 (90.3%)	0.01
Black	50 (1.7%)	30 (1.8%)	10 (2.2%)	0.02
Others	63 (2.2%)	46 (2.7%)	36 (7.5%)	0.04
Smoking	279 (9.9%)	189 (10.9%)	35 (7.3%)	0.03
Diabetes	54 (1.9%)	89 (5.1%)	54 (11.3%)	0.01
BMI (Kg/m^2)	27.04 ± 4.9	27.6 ± 4.5	27.4 ± 5.3	0.59

BMI: Body Mass Index

Table 2 - Averages of total PSA, IPSS and Prostate size of the 5015 men.

	40-49 years	50-59 years	60-70 years	p
Men	2813 (56%)	1726 (34.5%)	476 (9.5%)	0.01
Total PSA (ng/dL)	0.9 ± 0.7	1.2 ± 0.5	1.7 ± 1.5	0.01
IPSS ≤ 7	2797 (99.4%)	1642 (95.1%)	381 (80%)	0.03
IPSS > 7	16 (0.6%)	84 (4.9%)	95 (20%)	0.03
Prostate Size (grams)	25.2 ± 7.3	30.9 ± 11.2	38 ± 18.8	0.03
Suspicious DRE	17/2813	63/1726	50/476	0.02

IPSS: International Prostate Symptom Score; **DRE:** Digital Rectal Examination

Table 3 - Prevalence of PSA less than 2.5, PSA between 2.5 and 4.0, and PSA greater than 4.0ng/dL in the different aging groups.

	PSA< 2.5ng/dL	PSA 2.5 to 4.0ng/dL	PSA>4.0ng/dL	p
Age				
40-49 years	2763 (98.2%)	35 (1.2%)	15 (0.6%)	0.01
50-59 years	1575 (91.2%)	108 (6.2%)	43 (2.6%)	0.03
60-70 years	385 (80.8%)	49 (10.2%)	42 (9%)	0.04
IPSS				
40-49 years	0.37 ± 0.1	0.6 ± 0.2	0.78 ± 0.4	0.01
50-59 years	1.01 ± 0.3	1.6 ± 0.5	2.4 ± 0.9	0.01
60-70 years	2.5 ± 0.7	2.4 ± 0.9	4.6 ± 1.9	0.01
Prostate Size				
40-49 years	25 ± 2.3	27 ± 4	29 ± 7	0.01
50-59 years	28 ± 3	30.2 ± 5	35 ± 3	0.01
60-70 years	32.5 ± 2	38.5 ± 5	43.7 ± 7	0.01
Free PSA ng/dL				
40-49 years		0.54 ± 0.2	0.69 ± 0.2	0.03
50-59 years		0.62 ± 0.15	0.77 ± 0.3	0.01
60-70 years		0.79 ± 0.4	0.83 ± 0.5	0.05

The Gleason score was 6 in 24 men (75%), and 7 in 8 men (25%). In the same way, 100 patients had PSA ≥ 4ng/mL. From these men, 80 were submitted to prostate biopsy. In this group, the predictive positive value of prostate biopsy was 40% (32/100). The Gleason score was 6 in 19 men (60%), 7 in 10 men (31%) and 8 in 3 men (9%). Regarding the treatment option of each patient, we do not have the follow-up. These data are presented in Table-4.

The second cutoff point used for statistical analysis was 1.5ng/mL. Out of 5015 men, 3978 (79.3%) had PSA less than 1.5ng/mL. As well as for 2.5ng/mL cutoff, the prevalence of PSA > 1.5ng/mL also increased with age, and was quite similar in men between the ages of 50 and 59, and greater than 60 years of age (38.6% and 36% respectively). These data are presented in Table-5.

DISCUSSION

The primary objective of this study was to evaluate the PSA levels in a large population of young Brazilian men submitted to a health check-up program. The second objective was to correlate the different PSA cutoff with age, prostate size, and urinary symptoms. The data was collected in Sao Paulo, Brazil, from one of the largest check up program ever performed in a private hospital. This study was obtained from a database of 5015 men between the ages of 40 and 70, with an average age of 49 years old. Most of the

subjects were white, non-smokers, without co--morbidities such as diabetes, and have no urological complaints. The averages of total PSA in the three different aging groups were 0.9ng/mL for men between the ages of 40 and 50; 1.2ng/mL for men between 50 and 60; and 1.7ng/mL for men greater than 60 years old. Out of 5015 men, 4820 (96.11%) had an IPSS less or equal to 7. The prevalence of PSA greater than 2.5ng/mL was 1.8% in men between the ages of 40 and

Table 4 - The prevalence of PSA greater or less than 1.5ng/dL and its correlation with IPSS and prostate size.

	40-49 years	50-59 years	60-70 years	p
N	2813	1726	476	
PSA < 1.5ng/dL	2612 (92.8)	1061 (62.4%)	305 (64%)	0.02
PSA > 1.5ng/dL	201 (7.2%)	665 (38.6%)	171 (36%)	0.02
Avg IPSS				
PSA < 1.5ng/dL	0.33 ± 0.1	0.95 ± 0.4	2.5 ± 1.3	0.03
PSA > 1.5ng/dL	0.64 ± 0.2	1.6 ± 0.7	3.8 ± 1.7	0.03
Avg Prostate Size				
PSA < 1.5ng/dL	23.3 ± 3	30.1 ± 5	30 ± 7	0.02
PSA > 1.5ng/dL	27 ± 8	33 ± 7	35.9 ± 9	0.01

Avg: Average; **IPSS:** International Prostate Symptom Score

Table 5 - The prevalence of PSA greater or less than 1.5ng/dL and its correlation with IPSS and prostate size.

	PSA < 1.5ng/dL	PSA > 1.5ng/dL	p
Age			
40-49 years	2612 (92.8%)	201 (7.2%)	0.02
50-59 years	1061 (62,4%)	665 (38.6%)	0.02
60-70 years	305 (64%)	171 (36%)	0.02
IPSS			
40-49 years	0.33 ± 0.1	0.64 ± 0.2	0.03
50-59 years	0.95 ± 0.4	1.6 ± 0.7	0.03
60-70 years	2.5 ± 1.3	3.8 ± 1.7	0.03
Prostate Size (grams)			
40-49 years	23.3 ± 3	27 ± 8	0.01
50-59 years	30.1 ± 5	33 ± 7	0.02
60-70 years	30 ± 7	35.9 ± 9	0.01

50; 8.8% between 50 and 60; and 11.1% after 60 years of age. Only 20.6% had a PSA level greater than 1.5ng/mL. The predictive positive value of prostate biopsy in men with PSA between 2.5 to 4ng/mL was 25% and all of them had Gleason score ≤ 7. In the same way, the predictive positive value of prostate biopsy in men with PSA ≥ 4ng/mL was 40% and 91% of them had Gleason score ≤ 7.

The primary goal of prostate cancer screening in this specific population of younger men is the early detection of prostate cancer. Regarding prostate screening programs, men can potentially fall into 1 of 3 categories: 1) those whose cancer will result in death despite early diagnosis and treatment; 2) those who will have good outcomes in the absence of screening; and 3) those for whom early diagnosis and treatment improve survival.

There is convincing evidence that with or without screening the number of men who survive prostate cancer after 10 to 14 years is, at best, very small (14, 15). In addition, the inevitability of overdiagnosis and overtreatment of prostate cancer as a result of screening means that many men will experience the adverse effects of diagnosis and treatment of a disease that would have remained asymptomatic throughout their lifetime. In accordance with the U.S. Preventive Services Task Force (USPSTF) statement of recommendations published in 2012, there is moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh its harmful effects (3).

False positive PSA test results are common and vary depending on the PSA cutoff and frequency of screening. After four PSA tests, men in the screening group of the PLCO trial had a 12.9% cumulative risk for at least 1 false positive result, and a 5.5% risk for at least 1 biopsy due to a false positive result. A false positive result has a negative impact on patient's quality of life (4, 14). The ProtecT study found that 32% of men submitted to a prostate biopsy experienced pain; fever; blood in the urine, semen, or stool; infection; transient urinary difficulties; or other issues that they considered a moderate or major problem (9).

In the present study, the majority of men was white and less than 50 years old. According to recent data, the recommendation of PSA screening in this specific population remains controversial. It is well established that age, race, and family history of prostate cancer increase the risk of developing and dying of the disease. Black men are approximately twice as likely to die of prostate cancer than other men, and the reason for this disparity is unknown (16). Preliminary results from PIVOT (Prostate Cancer Intervention Versus Observation Trial), in which 30% of enrollees were black, found no difference in outcomes due to treatment of prostate cancer in these men compared with other races (17). Despite controversies, the 2013 American Urological Association Guidelines recognized that the PSA screening test might benefit certain subgroups of younger men with high risk of prostate cancer. However, this report suggests that patients should be informed about the potential harmful effects of these tests as well as the benefits of screening at an earlier age. Physicians should be aware that there are no comparative data and the best approach for this specific group is not well established (18).

The PSA-based screening in men 50 to 74 years of age has been evaluated in 5 randomized, controlled trials with different cutoffs and screening intervals. The PLCO trial found a nonstatistically significant increase in prostate cancer mortality in the annual screening group at 11.5 and 13 years post diagnosis (4, 14). The ERSPC trial demonstrated a mortality ratio (RR) of 0.80 (95% CI, 0.65 to 0.98) in screened men after a median follow up of 9 years, with similar findings at 11 years (RR 0.79, CI 0.68 to 0.91) (5, 15). In the present study 2080 (41.4%) men were older than 50 years of age, 4723 (94.17%) had PSA less than 2.5ng/dL, and 3978 (79.3%) had PSA less than 1.5ng/dL.

In a prevalence study and clinical significance of prostate cancer among 12682 men with normal DRE and low PSA levels Pepe et al. have shown that 27.4% of men with PSA between 2.5 and 4ng/mL had prostate cancer and some of them were clinically significant (19). Another recent study published by Faria et al. evaluated the

detection rates, clinical and pathological findings in Brazilian men with serum PSA levels <4ng/mL. In this study the predictive positive value of prostate biopsy in men with PSA between 2.5 and 3.9ng/mL was 31.1%. All patients had clinical stage I and 96.8% had Gleason score ≤ 7. After radical prostatectomy, 82.4% had pathological stage T2 and 17.6% had pathological stage T3 (20). In our study we have found similar results regarding prostate biopsy predictive positive value. For patients with PSA between 2.5 and 3.9ng/mL, 25% had prostate cancer and all of them had Gleason score ≤ 7. On the other hand, the predictive positive value of prostate biopsy in patients with PSA ≥ 4ng/mL was 40% and 9% had Gleason score > 7.

The conventional PSA cutoff of 4.0ng/dL detects most cases of prostate cancer; however, some cases will be missed. Using a lower cutoff point detects more cases of cancer but at the cost of labeling more men as potentially having the disease. When the PSA cutoff decreases to 2.5ng/dL more than double the number of men aged 40 to 69, with abnormal results, show a false positive result. This cutoff level also increases the likelihood of detection of indolent tumors with no clinical importance. Conversely, increasing the PSA cutoff to a level greater than 10ng/dL would reduce a prostate cancer diagnosis in the number of men aged 50 to 69 with abnormal results from 1.2 million to roughly 352,000. It is important to note there is no PSA cutoff at which a man can be guaranteed to be free from prostate cancer (21, 22).

Despite the benefits of this large population sample of Brazilian men who underwent this urological examination, the limitations of this study must be recognized. First, it was performed with patients referred to a private hospital, who have a good health insurance and a better medical care whether compared to the whole Brazilian population. Second, our database did not have patient family history information. Third, 60 cases with PSA between 2.5 and 2.9ng/dL, and 20 cases with PSA > 4.0ng/dL were not submitted to prostate biopsies. This precludes accurate conclusions regarding prostate cancer incidence in this population.

The idea of prostate screening implies that most asymptomatic prostate cancers could become clinically important and lead to poor health outcomes, and that early treatment could effectively reduce prostate cancer specifically and thereby reduce mortality rates overall. However, long-term, population based cohort studies, and randomized treatment trials of conservatively managed men with localized prostate cancer do not support this hypothesis (6).

Our database showed that the PSA level in Brazilian men submitted to a health check-up program was low. In this context, it should be emphasized that lower PSA levels do not exclude prostate cancer. According to some population-based studies, approximately 25% of men with PSA < 4.0ng/dL will have prostate cancer with Gleason score higher than 6.

The PSA level had a positive correlation with age, prostate size and prostate symptoms. Despite some of the limitations, we believe that this study provides substantial information about PSA screening tests performed in younger men from underdeveloped countries. To our knowledge this study represents the first urological Brazilian-database report carried out with this large number of patients.

ACKNOWLEDGEMENTS

Christina Ross, who participate on the manuscript elaboration and english grammar review.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 753-762, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.06

Preoperative serum albumin as a prognostic factor in patients with upper urinary tract urothelial carcinoma

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ABSTRACT

Purpose: The study evaluated whether preoperative measures of the C-reactive protein--based systemic inflammatory response may predict cancer survival independent of tumor stage in patients with upper urinary tract urothelial carcinoma (UTUC).

Materials and Methods: Between September 1999 and October 2010, 181 patients submitted to radical nephroureterectomy were available for evaluation. Multivariate survival analyses were performed using Cox's proportional hazards model and the coefficient for each factor was divided by the highest coefficient, multiplied by 4, and rounded to the nearest integer.

Results: Multivariate analyses showed that tumor location, pathologic T stage, lymphovascular invasion, margin status, and albumin level were independent contributors. The bootstrap-corrected C statistics of the model were 0.813 for disease-specific survival and 0.755 for overall survival, respectively. For time to disease-specific and overall mortality for patients, integrated area under the curve values were 0.792 and 0.739, respectively. When patients were clustered into three groups according to their model--predicted survival, the 5-year disease-specific survival in the low-, intermediate- and high-risk group was 95.4%, 76.2%, and 36.9%, respectively ($p<0.001$), and were 87.8%, 54.4%, and 31.8%, respectively, for overall survival ($p<0.001$). Decision curve analysis revealed that the use of model was associated with net benefit gains relative to the treat-all strategy.

Conclusions: Pretreatment albumin is a simple biomarker based on routinely available well-standardized measures, and is not an expensive and time-consuming process. Hypoalbuminemia is an independent marker of poor prognosis in patients with upper urinary tract urothelial carcinoma.

ARTICLE INFO

Key words:
Carcinoma, Transitional Cell; Urinary Tract; Ureter; C-Reactive Protein; Inflammation

Int Braz J Urol. 2014; 40: 753-62

Submitted for publication:
December 02, 2013

Accepted after revision:
April 06, 2014

INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) is a relatively rare malignancy, accounting for 5% of all urothelial carcinomas (1). Since these tumors often behave aggressively and local failure rates are high, even after radical surgical treatment, the outcome of patients with UTUC is still generally poor (1). Although tumor stage and histologic grade are the most significant prognostic factors for UTUC, the significance of other relevant factors, such as lymphovascular invasion, tumor necrosis, tumor architecture, and concomitant carcinoma in situ, are unclear (2).

Disease outcome in cancer patients is not solely determined by the local characteristics of the tumor. The host systemic inflammatory response (SIR) is also involved (3). As a state of chronic inflammation plays a role in the initiation, promotion, and progression of malignant disease

(4), host SIR may be an important tumor stage-independent predictor of outcome in cancer. Previous studies have established the prognostic importance of the SIR in patients with localized tumor undergoing curative surgery (5) as well as advanced tumors (6). Based on a previous study, C-reactive protein (CRP) level >10 mg/l (7), albumin level <35 g/l (7), and white cell count >11 x 10^9/l (8) were considered to indicate the presence of a SIR. In particular, CRP-based SIR have been explored and these prognostic scores have been associated with survival in patients with cancer: the combination of serum CRP and albumin as the original Glasgow prognostic score (9) and modified Glasgow prognostic score (10), and a combination of CRP and white cell count in the prognostic index (11).

To our knowledge, a few studies have evaluated the prognostic value of CRP-based SIR in patients with UTUC (12). The aim of this study was to evaluate whether preoperative measures of CRP-based SIR may predict cancer survival, independent of tumor stage, in patients with UTUC.

MATERIALS AND METHODS

Patient selection and data collection

The study protocol was approved by our Institutional Review Board. We retrospectively reviewed our database of the 303 patients who underwent radical nephroureterectomy for primary UTUC between September 1999 and October 2010. Exclusion criteria were: 1) no available laboratory data for inflammation, such as CRP, albumin, and white cell count; 2) clinical evidence of infection or inflammatory conditions, such as pneumonia, inflammatory bowel disease, or rheumatoid arthritis; 3) history of bladder tumor at a higher stage than the upper tract disease; 4) preoperative chemotherapy or irradiation; and 5) distant metastatic disease at the time of surgery. In total, 181 patients (median age 65.7 years, range 34.2-90.0 years) were available for evaluation. Median follow-up period of those patients was 56.4 months (range 0.1 to 158.0). The clinical and histologic criteria for these 181 patients are shown in Table-1.

Table 1 - Patient characteristics.

Variables	
Total	181
Gender (male/female)	144 (79.6)/37 (20.4)
Age, year (median, interquartile range)	65.7, 59.4-72.6
Body mass index, cm/kg^2 (median, interquartile range)	24.1, 22.2-25.8
Tumor location (renal pelvis/ureter/both)	86 (47.5)/67 (37.0)/28 (15.5)
Pathologic T stage (pTa/is/1/2/3/4)	22 (12.2)/1 (0.6)/43 (23.8)/35 (19.3)/76 (42.0)/4 (2.2)
Tumor grade (G1/2/3)	8 (4.4)/113 (62.4)/60 (33.1)
Lymph node stage (Nx/0/+)	147 (81.2)/26 (14.4)/8 (4.4)
Concomitant carcinoma in situ (absent/present)	164 (90.6)/17 (9.4)
Lymphovascular invasion (absent/present)	150 (82.9)/31 (17.1)
Margin status (negative/positive)	170 (93.9)/11 (6.1)
C-reactive protein, mg/l (≤10/>10)	137 (75.7)/44 (24.3)
Albumin, g/l (≥35/<35)	165 (91.2)/16 (8.8)
White Cell Count, 10^9/l (≤11/>11)	168 (92.8)/13 (7.2)
Glasgow Prognostic Score (0/1/2)	130 (71.8)/42 (23.2)/9 (5.0)
Modified Glasgow Prognostic Score (0/1/2)	137 (75.7)/35 (19.3)/9 (5.0)
Prognostic Index (0/1/2)	134 (74.0)/37 (20.4)/10 (5.5)

Data presented are number (%) or median (interquartile range).

The kidney, ureter, and bladder cuff were excised en bloc. A regional lymphadenectomy was performed when nodal involvement was suspected from the preoperative workup or was discovered during the procedure. Adjuvant cisplatin-based combination chemotherapy was administered in most patients with disease pT3 or pT4, and/or nodal involvement, but the decision for conducting adjuvant chemotherapy was left to the treating urologists.

Laboratory measurements

CRP, albumin, and white cell count were measured a few days prior to surgery as part of the routine examination. Routine laboratory measurements including the serum level of CRP, albumin, and white cell count were performed preoperatively. The coefficient of variation for these methods over the range of measurement was <5% as established by routine quality control procedures. The prognostic subdivisions used for each described prognostic score are consistent with the previously published literature (Table-2) (7-11).

Table 2 - Systemic inflammation-based prognostic scores.

Prognostic scores	Score
C-reactive protein[7]	
≤10 mg/l	0
>10 mg/l	1
Albumin[7]	
≥35 g/l	0
<35 g/l	1
White cell count[8]	
≤11 (10^9/l)	0
>11 (10^9/l)	1
Glasgow Prognostic Score[9]	
C-reactive protein ≤10 mg/l and albumin ≥35 g/l	0
C-reactive protein ≤10 mg/l and albumin <35 g/l	1
C-reactive protein >10 mg/l	1
C-reactive protein >10 mg/l and albumin <35 g/l	2
Modified Glasgow Prognostic Score[10]	
C-reactive protein ≤10 mg/l and albumin ≥35 g/l	0
C-reactive protein ≤10 mg/l and albumin <35 g/l	0
C-reactive protein >10 mg/l	1
C-reactive protein >10 mg/l and albumin <35 g/l	2
Prognostic Index[11]	
C-reactive protein ≤10 mg/l and white cell count ≤11 (10^9/l)	0
C-reactive protein ≤10 mg/l and white cell count >11 (10^9/l)	1
C-reactive protein >10 mg/l and white cell count ≤11 (10^9/l)	1
C-reactive protein >10 mg/l and white cell count >11 (10^9/l)	2

Pathologic analysis

All surgical specimens were examined by a dedicated genitourinary pathologist and processed according to standardized procedures. The TNM stage was determined according to the Union Internationale Contre le Cancer/American Joint Cancer Committee 2004 classification. The tumor grade was determined according to the World Health Organization 1973 and 2004 classifications (13). Lymphovascular invasion was defined as the presence of tumor cells in an endothelium-lined space but not in the underlying muscular walls. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any upper urinary tract location. Positive margin status was defined as tumor presence at linked areas of soft tissue on the surgical specimen.

Postoperative follow-up

Patients were generally followed every 3-4 months for the first 2 years, every 6 months in years 3 and 4, and annually thereafter. Follow-up examinations included a history, physical examination, blood laboratory tests, urine cytology, cystoscopic evaluation, chest radiography, and abdomino-pelvic computed tomography (CT). Oncological outcome analyses focused on disease-specific survival (DSS). Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Patient data were censored at

the last follow-up or death if the event of interest had not been attained. All patients who were identified as having died of UTUC had progressive and widely disseminated metastases at the time of death. Patients who died in the perioperative period within 30 days of surgery were censored at time of death for DSS analyses.

Statistical analysis

Data are presented as median and interquartile range. Several variables were chosen, including gender, patient age, body mass index, pathologic T stage, tumor grade, lymph node stage, concomitant carcinoma in situ, lymphovascular invasion, margin status, CRP, albumin, white cell count, Glasgow prognostic score, modified Glasgow prognostic score, and prognostic index. Multivariate survival analysis with calculation of hazard ratio (HR) with 95% confidence interval (CI) was performed using the Cox proportional hazards model including all covariates that were significant on univariate analysis. We applied a weighting method to each variable (14); the coefficient for each factor was divided by the highest coefficient, multiplied by 4, and rounded to the nearest integer (15). Precision of the reported coefficients was assessed by creating 1,000 bootstrap samples from the entire data set and replicating the estimation process. CIs were obtained using this bootstrap method of the corresponding sampling distributions.

To evaluate the performance of the models, we assessed these models in terms of both discrimination and calibration (16). The discriminative ability of the model was measured quantitatively using the C statistic (17) and time-dependent receiver operating characteristics curve (18). A score was calculated for each patient by adding together the points corresponding to his or her factors, and the patients were divided into three groups on the basis of the score. The survival stratified by risk groups was calculated using the Kaplan--Meier method. Calibration was also assessed by the calibration plot. To determine the net benefit, we relied on decision curve analysis (19).

For all statistical analyses, two-sided $p<0.05$ was regarded as significant. Analysis was performed using SPSS software (SPSS, Chicago, IL) and R 2.13.0 (R Development Core Team, Vienna, Austria, http://www.R-project.org).

RESULTS

Table-3 shows the results of the multivariate Cox regression analyses in the cohort related to survival. Univariate analysis revealed that tumor location, pathologic T stage, tumor grade, lymph node stage, lymphovascular invasion, margin status, and albumin level were significant predictors of disease-specific survival. Multivariate analysis with these variables as covariates showed that tumor location, pathologic T stage, lymphovascular invasion, margin status, and albumin level were independent contributors. The score for DSS was calculated as 2 (if tumors located in both renal pelvis and ureter) + 3 (if pT2) or 4 (if ≥pT3) + 3 (if lymphovascular invasion) + 4 (if positive margin) + 2 (if albumin <35 g/l) and 0 (otherwise). In univariate analysis, tumor location, pathologic T stage, tumor grade, lymph node stage, lymphovascular invasion, margin status, CRP, and albumin level were significantly associated with overall survival (OS). Tumor location, pathologic T stage, lymphovascular invasion, margin status, and albumin level were independent contributors in the Cox regression model for OS. The score for OS was calculated as 2 (if tumors located in both renal pelvis and ureter) + 3 (if ≥pT3) + 3 (if lymphovascular invasion) + 4 (if positive margin) + 3 (if albumin <35 g/l) and 0 (otherwise) (Table-3).

Model discrimination was good for both models. The bootstrap-corrected C statistics of the multivariate Cox regression model were 0.813 (95% CI, 0.761-0.865) for DSS and 0.755 (95% CI, 0.702-0.807) for OS, respectively. To determine the accuracy of DSS and OS by the Cox regression model over the course of a follow-up period, we completed a concordance summary (integrated area under the curve). For time to disease-specific and overall mortality for patients, integrated area under the curve values were 0.792 and 0.739, respectively (Figure-1). Figure-2 illustrates the Kaplan-Meier curves for patients stratified into three groups from the models. Patients were clustered into three groups according to their model-

Table 3 - Multivariate Cox proportional hazard regression analysis of survival and scoring system based on regression coefficient.

	Disease-specific survival				Overall survival			
	p	HR (95% CI)	Coefficient (95% CI)*	Score†	p	HR (95% CI)	Coefficient (95% CI)*	Score†
Tumor location								
renal pelvis		reference				reference		
ureter	0.163	1.66 (0.82-3.36)			0.317	1.34 (0.75-2.39)		
both	0.006	3.06 (1.38-6.79)	1.12 (0.16-2.63)	2	0.009	2.29 (1.23-4.25)	0.83 (0.12-1.90)	2
Pathologic T stage								
pTa/is/1		reference				reference		
pT2	0.008	4.37 (1.47-13.02)	1.48 (0.49-3.32)	3	0.114	1.92 (0.86-4.31)		
pT3/4	<0.001	6.21 (2.38-16.21)	1.83 (1.07-3.39)	4	<0.001	3.27 (1.72-6.24)	1.19 (0.62-2.03)	3
Grade								
G1/2		reference				reference		
G3	0.239	1.44 (0.79-2.68)			0.515	1.18 (0.71-1.97)		
Lymph node stage								
Nx/0		reference				reference		
N+	0.790	0.85 (0.27-2.75)			0.668	0.79 (0.26-2.37)		
LVI								
Absent		reference				reference		
Present	<0.001	4.68 (2.41-9.10)	1.54 (0.88-2.46)	3	<0.001	3.46 (1.96-6.11)	1.24 (0.74-2.04)	3
Margin status								
negative		reference				reference		
positive	<0.001	5.24 (2.09-13.14)	1.66 (0.39-2.92)	4	<0.001	4.25 (1.98-9.09)	1.45 (0.56-2.35)	4
CRP, mg/l								
≤10						reference		
>10					0.470	1.24 (0.69-2.22)		
Albumin, g/l								
≥35		reference				reference		
<35	0.013	2.97 (1.25-7.03)	1.09 (-0.08-2.34)	2	0.016	2.48 (1.18-5.21)	0.91 (-0.09-1.89)	3

HR: hazard ratio, CI: confidence interval, LVI: lymphovascular invasion, CRP: C-reactive protein.
*Bootstrap results are based on 1,000 bootstrap samples.
†Assignment of points to risk factors was based on a linear transformation of the corresponding ß regression coefficient. The coefficient of each variable was divided by the highest coefficient, multiplied by 4, and rounded to the nearest integer.

Figure 1 - Time-dependent receiver operating characteristics curve analysis of the Cox regression model. Curve plots the area under the curve over time. (A) Disease-specific survival. Integrated AUC value was 0.792. (B) Overall survival. Integrated AUC value was 0.739.

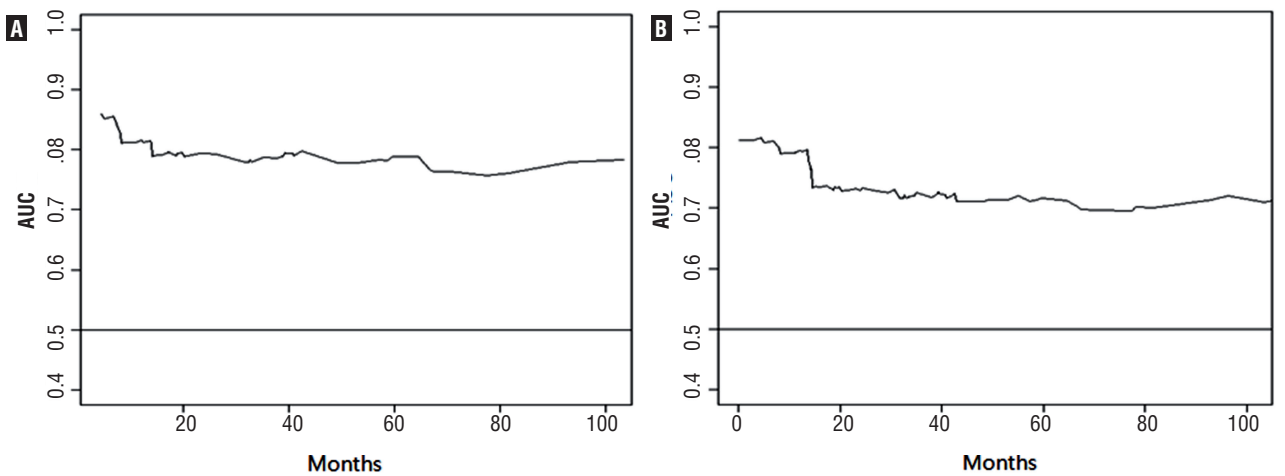
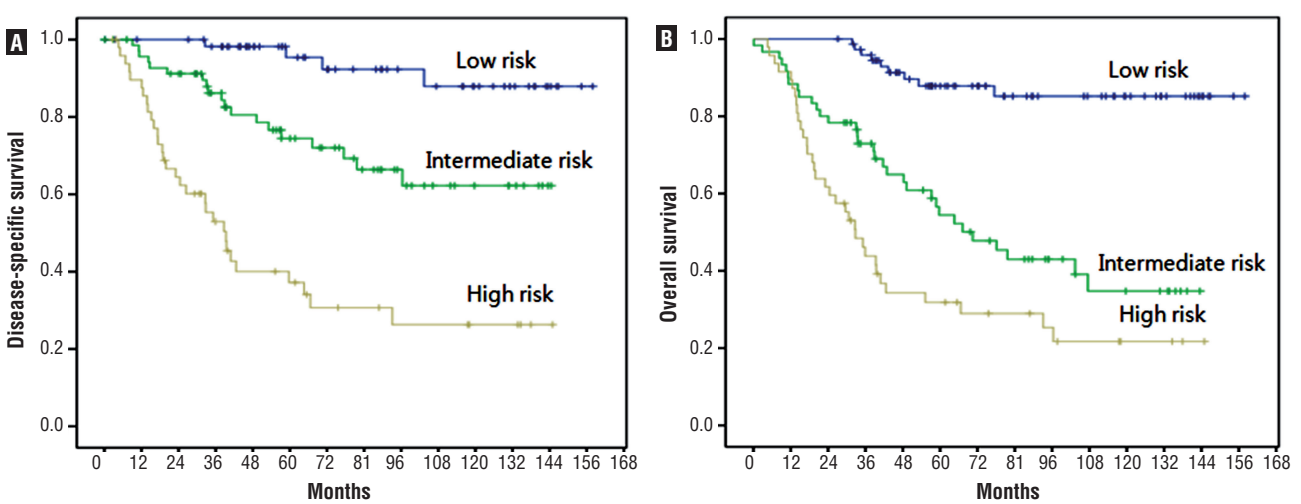


Figure 2 - (A) Kaplan-Meier plots of disease-specific survival of the Cox regression mode (p <0.0001). (B) Kaplan-Meier plots of overall survival of the Cox regression mode (p <0.0001).



-predicted survival (first quartile, <33%; second quartile, 33% to 66%; third quartile, >66%). As depicted, models discriminated well and log-rank test were all highly significant (p<0.001). According to the models, the 5-year DSS in the low-, intermediate-, and high-risk group was 95.4%, 76.2%, and 36.9%, respectively (Figure-2A), and 87.8%, 54.4%, and 31.8%, respectively, for OS (Figure-2B). To assess the agreement between the predicted and actual outcomes, we generated calibration curves. The dashed line represents the performance of an ideal model, where the predicted outcome would correspond perfectly with the actual outcome. The performance of model is plotted as the solid line. The models were reasonably calibrated (Figure-3). Figure-4 presents the results of the decision curve analysis at 5 years. In our cohort, the predictions resulted in good net benefit across the range of risk thresholds. Decision curve analysis revealed that the use of model was associated with net benefit gains relative to the treat-all strategy. The models performed well across a wide range of threshold probabilities using decision curve analysis.

Figure 3 - (A) Calibration curves for 5-year disease-specific survival predictions. (B)

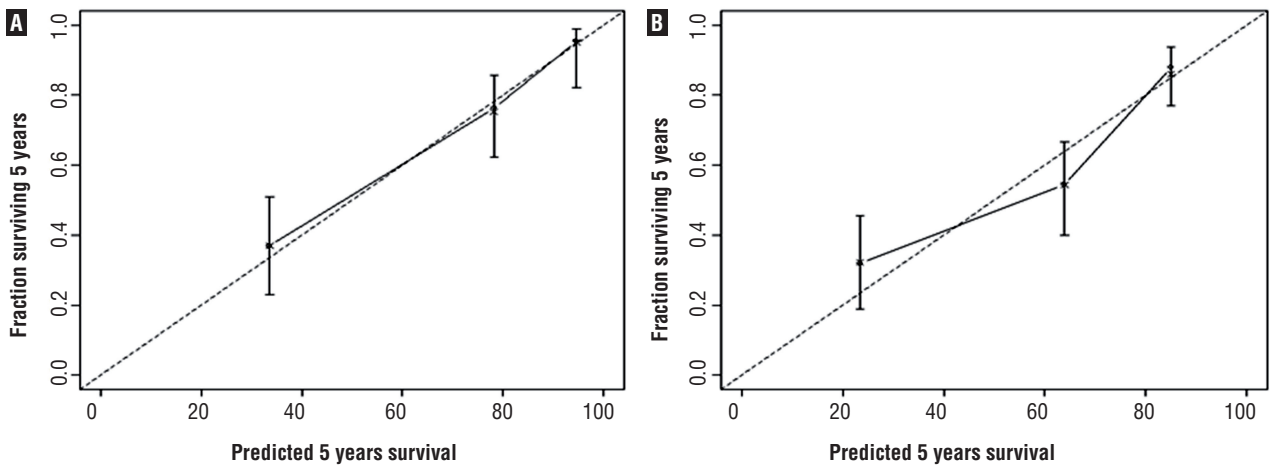
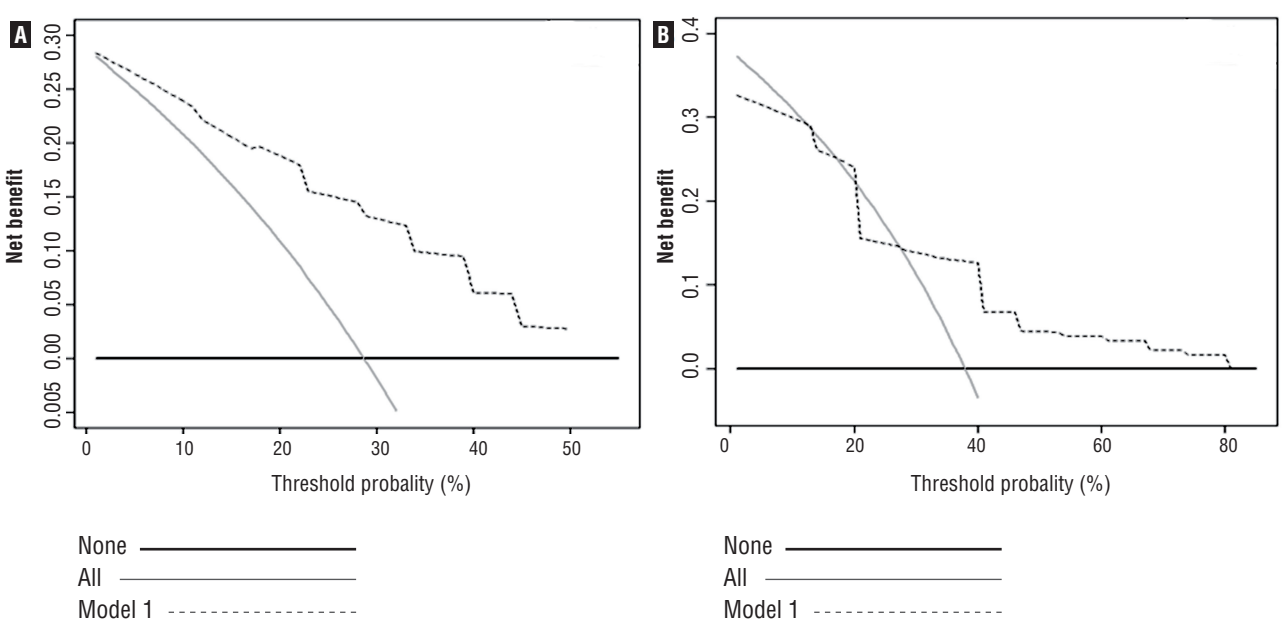


Figure 4 - Decision curve analysis for 5-year survival predictions. (A) Disease-specific survival. (B) Overall survival. In decision curve analysis, the y-axis measures net benefit, calculated by summing the benefits (true positives) and subtracting the harms (false positives). The straight line represents the assumption that all patients will die and the horizontal line represents the assumption that no patients will die. The dotted line indicates the net benefit of using the new model.



DISCUSSION

The prognosis of patients with UTUC remains unsatisfactory because it is one of the most aggressive carcinomas. Knowledge about prognosis is essential for patients and clinicians whenever multimodal treatment is considered. At present, no biomarker has been applicable for predicting the outcomes in patients with UTUC. There is increasing evidence that the presence of SIR is associated with poor outcome in patients undergoing resection for a variety of common solid tumors.

It has been proposed that there are intrinsic pathways involved in cancer-related inflammation, such as the induction of genetic instability by inflammatory mediators. A recent review proposed that cancer-related inflammation is the seventh hallmark of cancer (3). Inflammation in the tumor microenvironment plays an important role in tumor proliferation and the survival of malignant cells, and promotes tumor angiogenesis, invasion, and metastasis (4).

Recent definitions of cancer cachexia include elevation of CRP and hypoalbuminemia (20). CRP is an acute phase reactant that acts as a surveillance molecule for the activation of the adaptive immune system. It is considered a nonspecific but sensitive marker of systemic inflammation and has been related to most of the signs of nutritional depletion (21). Albumin represents a negative acute phase protein and its level decreases as CRP rises (22). Albumin is no longer considered as a nutritional marker, but rather is considered an inflammatory response marker (23). Increased catabolism, chronic malnutrition, and a chronic inflammatory reaction due to cancer eventually lead to hypoalbuminemia. Hypoalbuminemia may be due to the production of cytokines, such as interleukin-6, which modulates the production of albumin by hepatocytes (24). Alternatively, tumor necrosis factor may increase the permeability of the microvasculature, allowing an increased transcapillary passage of albumin (25). Also, the presence of micrometastatic tumor cells in liver may induce Kuppfer cells to produce a variety of cytokines, which may modulate albumin synthesis by hepatocytes (24,26).

Hypoalbuminemia provides additional prognostic information for patients with cancer in various organs. Hypoalbuminemia is predictive of increased 90-day mortality and poor overall survival after radical cystectomy in patients with bladder cancer (27). In patients with hepatocellular carcinoma, hypoalbuminemia is an independent poor prognostic factor (28). Separate studies reported that preoperative hypoalbuminemia is associated with earlier tumor recurrence and death following potentially curative resection for colon and rectal cancer (24,29). Hypoalbuminemia as a marker of the SIR and not CRP is a significant and independent predictor of survival in patients with primary operable breast cancer (30).

It is not yet established if any specific component of SIR is a better predictor of cancer survival. This study is the first to show hypoalbuminemia to be superior to other CRP-based SIR prognostic scores for the prediction of prognosis in patients with UTUC. Presently, among the inflammation-based prognostic scores, only albumin was significantly associated with disease-specific survival and had prognostic value independent of TNM stage. This would suggest that albumin has superior prognostic value than other scores based on CRP (Glasgow prognostic score, modified Glasgow prognostic score, and prognostic index) in terms of outcome and should be used in preference to cellular markers of the SIR. Therefore, any further development of prognostic scores based on the SIR should include albumin. However, since the basis of the relationship between the SIR and poorer DSS in patients with UTUC is not clear, the cause-effect relationship between a SIR and DSS is questionable.

We used a wide array of tools to evaluate our multivariate Cox regression model including discrimination as well as calibration analyses. In addition, we used decision curve analysis to show the clinical net benefit. Our study results support the view that hypoalbuminemia has significant prognostic value. We observed a good prediction of clinical outcome by the model. The accuracy of the model for DSS and OS disease-specific and overall survival was 81.3% and 75.5%, respectively. The Kaplan-Meier curve was within the boundaries of predictions for each of the three strata. Using decision curve analysis, the model demonstrated net benefit gains for predictions of the examined end points at 5 years after radical nephroureterectomy.

The present cohort has a number of limitations. Despite the retrospective nature of the data collection, not all patients in our database had preoperative data on CRP-based SIR. Therefore, the patients were not necessarily representative of all patients with UTUC in general. A large-scale prospective validation study is needed to confirm the results.

However, despite the retrospective nature of the study and a relatively small number of pa-

tients in a single center, a homogeneous patient population was sufficient to indicate the significance of hypoalbuminemia as a postoperative prognostication of patients with UTUC.

CONCLUSIONS

In the present study, hypoalbuminemia predicted DSS as well as OS independent of stage in patients with UTUC. Pretreatment albumin is a simple biomarker based on routinely available well-standardized measures, is not expensive, and does not involve a time-consuming process. Our study demonstrates that hypoalbuminemia is an independent marker of poor prognosis in patients with UTUC and is superior to other CRP-based SIR protocols in terms of prognostic ability.

ABBREVIATIONS

CI = confidence interval
CRP = C-reactive protein
CT = computed tomography
DSS = disease-specific survival
HR = hazard ratio
OS =overall survival
SIR = systemic inflammatory response
UTUC = upper urinary tract urothelial carcinoma

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ORIGINAL ARTICLE

Vol. 40 (6): 763-771, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.07

Urine leak in minimally invasive partial nephrectomy: analysis of risk factors and role of intraoperative ureteral catheterization

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ABSTRACT

Purpose: To investigate risk factors for urine leak in patients undergoing minimally invasive partial nephrectomy (MIPN) and to determine the role of intraoperative ureteral catheterization in preventing this postoperative complication.

Materials and Methods: MIPN procedures done from September 1999 to July 2012 at our Center were reviewed from our IRB-approved database. Patient and tumor characteristics, operative techniques and outcomes were analyzed. Patients with evidence of urine leak were identified. Outcomes were compared between patients with preoperative ureteral catheterization (C-group) and those without (NC-group). Univariable and multivariable analyses were performed to identify factors predicting postoperative urine leak.

Results: A total of 1,019 cases were included (452 robotic partial nephrectomy cases and 567 laparoscopic partial nephrectomy cases). Five hundred twenty eight patients (51.8%) were in the C-group, whereas 491 of them (48.2%) in the NC-group. Urine leak occurred in 31(3%) cases, 4.6% in the C-group and 1.4% in the NC-group ($p<0.001$). Tumors in NC-group had significantly higher RENAL score, shorter operative and warm ischemic times. On multivariable analysis, tumor proximity to collecting system (OR=9.2; $p<0.01$), surgeon's early operative experience (OR=7.8; $p<0.01$) and preoperative moderate to severe CKD (OR=3.1; $p<0.01$) significantly increased the odds of the occurrence of a postoperative urine leak.

Conclusion: Clinically significant urine leak after MIPN in a high volume institution setting is uncommon. This event is more likely to occur in cases of renal masses that are close to the collecting system, in patients with preoperative CKD and when operating surgeon is still in the learning curve for the procedure. Our findings suggest that routine intraoperative ureteral catheterization during MIPN does not reduce the probability of postoperative urine leak. In addition, it adds to the overall operative time.

ARTICLE INFO

Key words:
complications [Subheading]; Nephrectomy; Risk Factors; Urinary Incontinence; Ureter; Urinary Catheters

Int Braz J Urol. 2014; 40: 763-71

Submitted for publication:
January 27, 2014

Accepted after revision:
April 06, 2014

INTRODUCTION

Partial nephrectomy (PN) has widely replaced radical nephrectomy in the management of renal neoplasms by offering renal functional preservation without compromising oncological outcomes (1). With widespread uptake of PN, complications unique to this surgery became more

recognized. Among them, postoperative urine leak is regarded as a clinically significant entity, which negatively impacts patient's recovery (2-5). Inadequate repair of a violated collecting system during renorrhaphy is the cause of postoperative urine leak. The management of urine leak is tailored depending on the case. The treatment options include observation, percutaneous drainage, ureteral drainage and surgical interventions (6-8).

Intraoperative ureteral catheterization during PN has been traditionally used as a measure to recognize and prevent the occurrence of urine leaks (9). The concept behind this practice was that intra-operative retrograde dilute methylene-blue instillation could confirm collecting system entry and water tightness of the repair. With accumulation of experience with the technique, routine ureteral cannulation was reserved for central, more complex renal tumors (10). Ureteral catheterization however adds to the total operative time and costs. With advancements in minimally invasive techniques for PN, the routine use of ureteral catheterization has been further questioned (11). Overall, the utility of routine ureteral catheterization during PN has not been well studied.

The aim of this study was to investigate risk factors for urine leak in patients undergoing minimally invasive partial nephrectomy (MIPN) and to determine the role of intraoperative ureteral catheterization in preventing this postoperative complication.

MATERIALS AND METHODS

Study population

Our IRB-approved prospectively maintained institutional database was queried to identify MIPN cases (laparoscopic and robotic) performed at our Center from September 1999 to July 2012.

Patients' demographic characteristics, including age, BMI, and ASA as well as tumor characteristics, including R.E.N.A.L nephrometry score (12) were assessed. Main intraoperative parameters, including technique modality (laparoscopic or robotic), use of ureteral catheterization, operative time (calculated from skin incision to skin closure, including ureteral catheterization time), warm ischemia time (WIT), and estimated blood loss (EBL) were recorded.

Cases with intraoperative ureteral injury were excluded. Patients with ureteral abnormality such as ureteropelvic junction obstruction or duplicated collecting were also excluded.

Surgical experience was taken into account in the analysis. Completion of the learning curve was considered to be 25 cases for RPN and 50 cases for LPN according to previous publications (13, 14).

Clinically significant urine leak was defined as persistent drain output >48 hours after PN with biochemical analysis consistent with urine or radiographic evidence of urine leak (15). Radiological imaging was only performed where patient's clinical status or symptoms were suggestive of urine leak (Figure-1).

Surgical technique

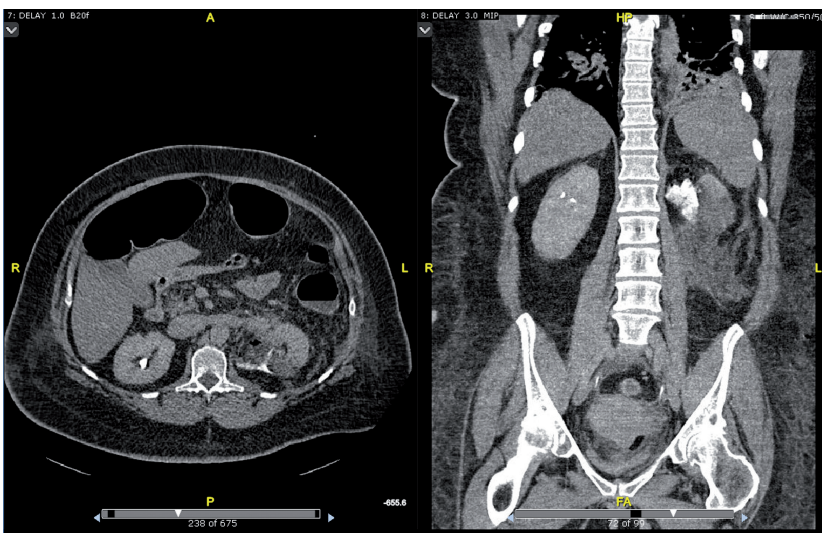
The decision for ureteral catheterization was at the discretion of surgeon on case by case basis. Ureteral catheterization was performed immediately after induction of general anesthesia with the patient in lithotomy position, using rigid cystoscopy. An open ended 6 French ureteral catheter was passed over the guide wire and catheter was secured to the Foley catheter. A syringe filled with dilute methylene blue was attached to the catheter for later instillation. The patient was then repositioned in the modified lateral decubitus position and PN commenced. Ureteric catheter was removed at the end of the procedure.

Our surgical techniques for both laparoscopic (LPN) and robot assisted PN (RPN) have been previously described (16, 17).

Essential steps of the laparoscopic technique include renal defatting, maintaining fat over the tumor, laparoscopic ultrasound to score the resection line, hilar clamping, tumor excision with cold scissors, suture repair of the collecting system and sutured renorrhaphy over a hemostatic bolster.

The robotic technique included tumor identification under ultrasound guidance and its demarcation, hilar clamping, tumor excision, closure of the kidney defect using two layers of horizontal mattress sutures, one to close entries to the collecting system and the other to approximate the renal capsule (17). Early in our robotic experience, standard interrupted bolstered renorrhaphy was used for capsule closure (18).

Figure 1 - Axial and coronal CT images documenting left urine leak after surgery.



For both laparoscopic and robotic cases, a Jackson-Pratt drain was left in the perinephric space.

Analysis

Estimated glomerular filtration rate (eGFR) was calculated using modification of diet in renal disease (MDRD) formula. Moderate to severe chronic kidney disease (CKD) was defined as eGFR<60mL/min/1.73m^2.

For continuous data with normal distribution variables are presented as mean±standard deviation (SD). The mean values were compared using student's t-test. For variables with non-normal distribution, data is presented as median (IQR) and the groups were compared using Mann-Whitney U test. Categorical variables were compared using chi-squared test.

A comparative analysis was performed between the group where a ureteral catheter was used (C group) and the one where this was not used (NC group).

Univariable and multivariable logistic regression analyses were performed to calculate odd ratios for factors affecting urinary leak. These included surgical technique (laparoscopic or robotic), learning curve (beyond or within), age (continuous), BMI (continuous), renal function (moderate to severe CKD vs. mild CKD to normal renal function), tumor size (continuous), growth pattern (>or<50% endophytic), proximity to collecting system (>or<7mm), WIT (continuous), EBL (continuous) and use of intraoperative ureteral catheterization (yes or no).

Statistical significance was set at p<0.05. Variables were entered into multivariable model if p<0.2 for univariable analysis. All analyses were performed using SPSS v21 software (IBM SPSS Statistics, Armonk, NY: IBM Corp).

RESULTS

A total of 1019 MIPN cases were considered in this analysis, including 567 LPN cases (55.6%) and 452 RPN cases (44.4%) (Table-1).

Table-2 summarizes the main surgical outcomes for the entire series. In 528 cases (51.8%) intra-operative ureteral catheterization was used. A total of 31 (3.0%) urine leaks were detected postoperatively and managed using stenting, CT-guided drainage or observation.

There were no differences in the patients' age, gender, BMI, ASA, renal function, tumor laterality and solitary kidney status between C-group and NC-group (Table-3). Tumors in the C-group presented a lower overall R.E.N.A.L nephrometry score, longer distance from the collecting system, smaller size and more exophytic location compared to NC-group. The majority of cases in C-group

Table 1 - Population Demographics (n=1019).

Variable		Value
Age, years	Mean±SD	59.1±12.4
ASA	Median (IQR)	3 (1)
BMI, kg/m²	Mean±SD	29.9±7
Tumor Laterality, n (%)	Right	552 (54.2)
	Left	467 (45.8)
Tumor Size, cm	Median (IQR)	2.5 (1.7)
Technique, n (%)	Laparoscopic	567 (55.6)
	Robotic	452 (44.4)
Preoperative GFR, mL/min/1.73m²	Median (IQR)	81.1 (29.8)
RENAL Nephrometry Score	Median (IQR)	6 (3)
Solitary Kidney, n (%)		42 (4.1)

ASA: American Society of Anesthesiologists; **GFR:** Glomerular Filtration Rate; **BMI:** Body Mass Index; **SD:** Standard Deviation; **IQR:** Inter-Quartile Range.

Table 2 - Surgical Outcomes (n=1019).

Variable		Value
Intra operative Ureteral Catheterization, n (%)		528 (51.8)
Operative Time, min	**Mean±SD**	196.9±59.7
Unclamped Renal Hilum, n (%)		71 (7)
Warm Ischemia Time, min	**Median (IQR)**	26(15)
Zero Ischemia, n (%)		68 (6.7)
Estimated Blood Loss, mL	**Median (IQR)**	150 (200)
Urine Leak, n (%)		31 (3)
Urine Leak Management, n (%)	**Ureteral Stenting**	19 (61.3)
	CT-guided Drainage	3* (9.7)
	Observation	11 (35.5)
Length of Stay, days	**Median (IQR)**	3 (2)
Follow up, months	Median (IQR)	18 (34)

*Two of those had also ureteral stents and counted also in that group
SD: Standard Deviation, **IQR:** Inter-Quartile Range.

Table 3 - Comparison between Populations under Study (n=1019).

Variable		C-Group (n=528)	NC-Group (n=491)	p-Value
Technique, n (%)	Laparoscopic	468 (88.6)	99 (20.2)	0.001
	Robotic	60 (11.4)	392 (79.8)	
RENAL Nephrometry Score, median (IQR)		6 (2)	7 (4)	0.001
Cases performed by surgeons during learning curve, n (%)		124 (23.5)	64 (13)	0.001
Tumor size > 4cm, n (%)		67 (12.7)	102 (20.8)	0.001
Tumor growth pattern >50% endophytic, n (%)		190 (39.8)	201 (46.6)	0.03
Nearness to CS or Sinus < 7mm, n (%)		206 (42.4)	219 (50.8)	0.01
Operative Time, min, mean±SD		210.6±63.5	180.5±50.1	0.001
Warm Ischemia Time, min, median (IQR)		31 (13)	20 (12)	0.001
Urine Leak, n (%)		24 (4.6)	7 (1.4)	0.001

C-Group: Ureteral Catheterization used; **NC-Group:** Ureteral Catheterization not used; **CS:** Collecting System; **BMI:** Body Mass Index; **ASA:** American Society of Anesthesiologists

were done laparoscopically, whereas only 20% were done laparoscopically in NC-group (88.6% vs. 20.2%, p=0.001). The operative time was longer for patients in C-group (211 vs. 180 min, p<0.01). Once we control for ureteric catheterization, there is no difference in operating time between LPN and RPN (186±51.2 vs.178±49.5 min, p=0.17). There were 24 (4.6%) cases of urine leak in C-group as compared to 7 (1.4%) cases in NC-group (p=0.001). For LPN cases there was no difference in practice of ureteric catheter insertion with increasing experience. The rate of utility of ureteric catheter was 80.2% for surgeons within and 83% for surgeons beyond learning curve (p=0.49). For RPN group, this proportions were 49.4% and 4.7 % respectively (p=0.001) (Figure-2).

On univariable analysis, use of laparoscopy, presence of moderate to severe CKD, tumor nearness to collecting system or renal sinus, EBL and use of ureteral catheter had significantly higher odds of urine leak (Table-4).

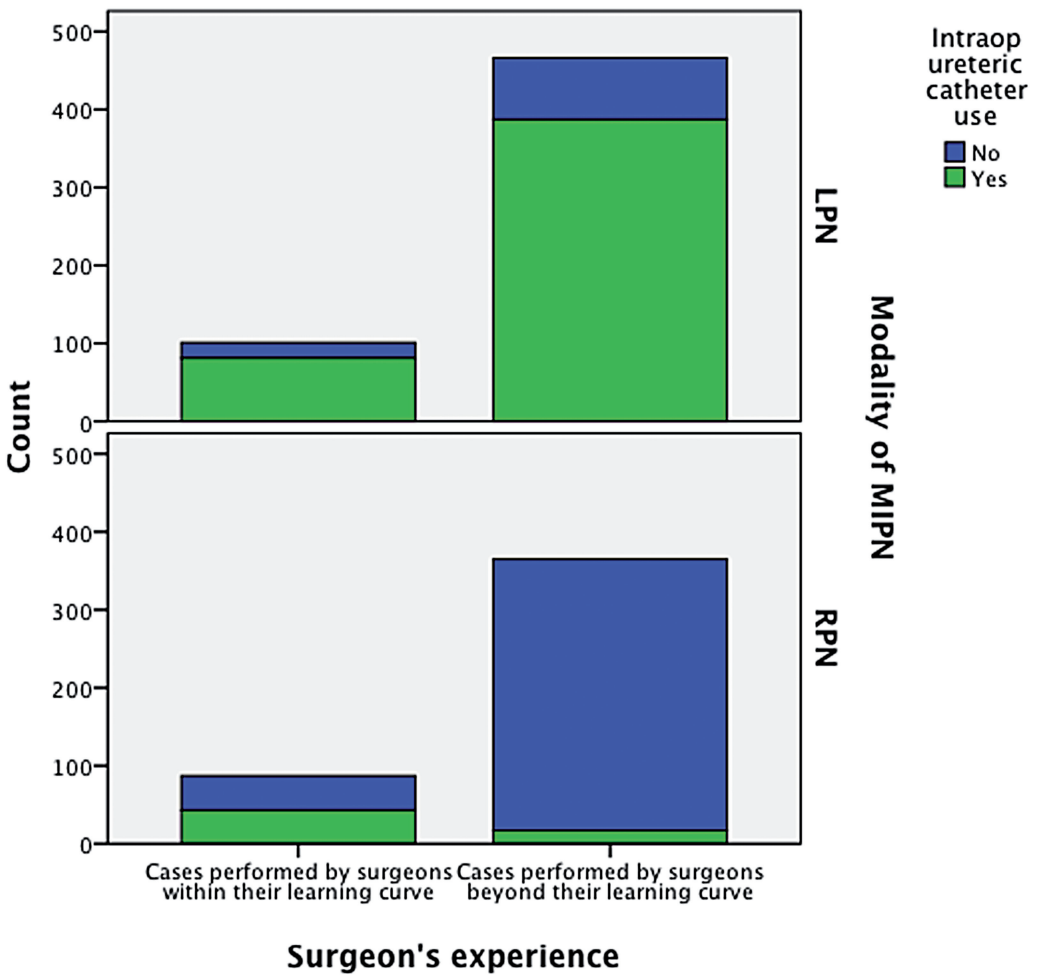
On multivariable analysis, (Table-4), nearness of the tumor to collecting system (OR=9.2; p=0.003), early surgeon's experience (OR=7.8; p=0.001), moderate to severe CKD (OR=3.1; p=0.04) and EBL (OR 1.002; p=0.003) were associated with higher urine leak occurrence. Intraoperative ureteral catheterization had no significant effect on urine leak occurrence (OR=1.3; p=0.67).

DISCUSSION

Urine leak is related to an incomplete repair of the collecting system at the time of renorrhaphy and it potentially represents a clinically significant complication of PN procedure (2-5). The reported incidence rate of urine leak post PN varies among institutions. Despite being low at high volume centers (3), as confirmed in the present analysis, it may result in considerable morbidity and financial cost.

Management of urine leak after PN is varied according to the clinical scenarios (8). Observation is the most conservative approach with serial cross sectional imaging at given time intervals. In other situations, selective placement of a ureteral stent facilitates drainage of urine from the collecting system and creates a low-pressure system that promotes healing of the defect. Complicated urine leaks may

Figure 2 - Bar graphs demonstrating the rate of employment of intraoperative ureteric catheter according to surgeon's experience for both LPN and RPN.



require invasive procedures, such as percutaneous drainage or surgical re-intervention. Investigational less invasive avenues are being explored, such as retrograde injection of sealant through the ureteral stent (6).

Routine intraoperative ureteral catheterization during PN has been used as an intra-operative measure to minimize the risk of urine leak. This practice has been carried from early open PN to LPN and even early RPN experience (9, 18, 19). Ureteral catheterization is time consuming, incurs additional cost and is not without risk of complications.

The decision for pre-operative ureteral catheterization in our series was based on surgeon's preference on case-by-case basis. This was also influenced by the minimally invasive modality and surgeon's own experience with that modality. For LPN cases, the use of ureteral catheter was not influenced by surgeon's experience or tumor complexity. For RPN cases ureteral catheter was inserted in 49.4% of cases performed within the surgeons' learning curve and only in 4.7% of cases beyond that. This was the case despite an increase in overall tumor complexity.

Compared to RPN, tumors treated with LPN were less complex and had lower R.E.N.A.L nephrometry scores. This trend has been observed by other series (20). Surgeons experience with the modality of MIPN treatment affected the rate of urinary leak regardless of tumor complexity score (apart from the degree of endophytic growth) and

Table 4 - Univariable and Multivariable Analysis of factors predicting postoperative urine leak.

Variable	Univariable Analysis				Multivariate Analysis			
	OR	95% CI		p-value	OR	95% CI		p-value
Laparoscopic vs. Robotic	2.3	1	5.3	0.04	1.29	0.3	5.6	0.73
Age	1	0.97	1.02	0.95				
Learning Curve (within vs. beyond)	1.84	0.8	4	0.13	7.8	2.5	24.3	**0.001**
BMI	1.03	0.99	1.07	0.13	1.06	0.99	1.13	0.07
Charlson Comorbidity Index	1.09	0.9	1.3	0.38				
Preop GFR (<60 vs. ≥60mL/min/1.73m²)	2.2	1.0	4.7	**0.049**	3.13	1.06	9.3	**0.04**
RENAL score	1.19	0.95	1.5	**0.13**				
REAL score (N removed)	1.19	0.95	1.5	**0.13**	0.91	0.62	1.3	0.62
Tumor Size (> 4 vs. ≤4cm)	1.2	0.5	3.0	0.67				
Tumor Growth (>50% vs. ≤50% endophytic)	1.0	0.4	2.4	0.99				
Nearness to CS or Sinus (<7mm vs. ≥7mm)	2.6	1.2	5.5	**0.01**	9.2	2.1	40.2	**0.003**
Ureteral Catheterization (presence vs. absence)	3.3	1.4	7.7	**0.006**	1.3	0.32	5.6	0.67
WIT	1	0.97	103	0.96				
Zero ischemia (Yes vs. No)	1.6	0.47	5.4	0.45				
EBL	1.001	1	1.002	**0.001**	1.002	1	1.003	**0.003**

CS: Collecting System; **OR:** Odds Ratio; **CI:** Confidence Interval; **BMI:** Body Mass Index; **Preop:** Preoperative,

use of intraoperative ureteral catheter. Kidneys operated during the surgeons' learning curve, had 7.8 fold higher probability of developing urine leak (p=0.001).

Proximity of the tumor to the collecting system also increased the odds of urine leak (OR=9.2; p=0.003). This is not surprising as a complete excision of these tumors, without entering the collecting system is not possible. This in turn, increases the likelihood of subsequent urine leak. This has been previously reported in large multi-institutional series (3, 21). Bruner et al. identified tumor's R.E.N.A.L nephrometry score was associated with risk of urine leak after PN (10). The authors reported that for each unit increase in R.E.N.A.L nephrometry the odds of urine leak increased by 35% (OR 1.35; 95% CI 1.08-1.69; P=0.009).

Presence of moderate to severe CKD was also found to be associated with increased likelihood of urine leak (OR=3.1; p=0.04). CKD has long been associated with poor wound healing (22) and this is a possible explanation for our finding.

On multivariable regression, the use of intraoperative ureteral catheterization was not a significant factor toward developing (or preventing) collecting system leak (p=0.19). EBL increased the odds of urinary leak, and this is likely a surrogate for complexity of surgery.

The rate of urine leak in contemporary PN series is around 1-5% (3, 23, 24). Kundu et al. reported that larger tumor sizes, higher estimated blood loss and longer ischemia time were associated with fistula formation. Apart from EBL, we did not identify any associated of urine leak with these factors in our cohort.

The operative time was longer for patients in C-group (211 vs. 180 min, $p<0.01$). Given smaller and less complex tumors in C-group, the ureteric catheterization is the likely reason for increase in operating time observed in this group.

On univariable analysis, RPN had significantly lower rate of urine leak compared to LPN group, but on multivariable analysis the groups were comparable despite more complex tumors in the RPN group. Given the small number of events (31 leaks) and differences in complexity of the tumors between the RPN and LPN groups, it is difficult to reach a definite conclusion on this. However, it can be speculated that the better vision offered by robotic console and the articulation ability of robotic instruments facilitate better identification and repair of the breached collecting systems (25, 26). This could be another explanation with regards to decrease utility of intraoperative ureteral catheter in the robotic cohort.

Bove et al. concluded that in selected group of patients (n=103) with small (mean size <3cm) renal mass undergoing LPN, routine use of ureteral catheter is not indicated (11). We have confirmed this finding in a large (n=1019) series of LPN and RPN cases, with 425 of patients having tumors in close proximity to collecting system and 169 patients having tumor sizes >4cm.

Lack of randomization, heterogeneous nature of the series and retrospective aspect of data are the main limitation of our series. Moreover, the small number of events further limits the analysis. In addition, the large volume nature of our center's experience with PN might limit the applicability of our findings to other settings. Despite these, we believe that our results provide the answer to the question of routine ureteral catheter use in PN. Lastly, it was outside the scope of the present study to perform a formal cost-analysis, so it remains to be demonstrated whether additional cost and time for ureteral catheterization outweighs the cost involved in the management of urine leaks eventually occurring postoperatively.

CONCLUSIONS

Clinically significant urine leak after MIPN in a high volume institution setting is uncommon. This event is more likely to occur in cases of renal masses that are close to the collecting system, in patients with preoperative CKD and when operating surgeon is still in the learning curve for the procedure. Our findings suggest that routine intraoperative ureteral catheterization during MIPN does not reduce the probability of postoperative urine leak. In addition, it adds to the overall operative time.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 772-780, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.08

What is the Incidence of Kidney Stones after Chemotherapy in Patients with Lymphoproliferative or Myeloproliferative Disorders?

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ABSTRACT

Introduction: This study describes the incidence and risk factors of de novo nephrolithiasis among patients with lymphoproliferative or myeloproliferative diseases who have undergone chemotherapy.

Materials and Methods: From 2001 to 2011, patients with lymphoproliferative or myeloproliferative disorders treated with chemotherapy were retrospectively identified. The incidence of image proven nephrolithiasis after chemotherapy was determined. Demographic and clinical variables were recorded. Patients with a history of nephrolithiasis prior to chemotherapy were excluded. The primary outcome was incidence of nephrolithiasis, and secondary outcomes were risk factors predictive of de novo stone. Comparative statistics were used to compare demographic and disease specific variables for patients who developed de novo stones versus those who did not.

Results: A total of 1,316 patients were identified and the incidence of de novo nephrolithiasis was 5.5% (72/1316; symptomatic stones 1.8% 24/1316). Among patients with nephrolithiasis, 72.2% had lymphoproliferative disorders, 27.8% had myeloproliferative disorders, and 25% utilized allopurinol. The median urinary pH was 5.5, and the mean serum uric acid, calcium, potassium and phosphorus levels were 7.5, 9.6, 4.3, and 3.8 mg/dL, respectively. In univariate analysis, mean uric acid (p=0.013), calcium (p<0.001)), and potassium (p=0.039) levels were higher in stone formers. Diabetes mellitus (p<0.001), hypertension (p=0.003), and hyperlipidemia (p<0.001) were more common in stone formers. In multivariate analysis, diabetes mellitus, hyperuricemia, and hypercalcemia predicted stone.

Conclusions: We report the incidence of de novo nephrolithiasis in patients who have undergone chemotherapy. Diabetes mellitus, hyperuricemia, and hypercalcemia are patient-specific risk factors that increase the odds of developing an upper tract stone following chemotherapy.

ARTICLE INFO

Key words:
Urolithiasis; Chemotherapy, Adjuvant; Calculi; Kidney Calculi; Ureteral Calculi

Int Braz J Urol. 2014; 40: 772-80

Submitted for publication:
March 05, 2014

Accepted after revision:
June 23, 2014

INTRODUCTION

Tumor lysis syndrome (TLS) is an oncologic emergency observed among patients with hematologic malignancies associated with significant morbidity/mortality if untreated. TLS occurs when tumor cells release their contents into the bloodstream, either spontaneou-

sly or after chemotherapy, leading to hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia (1). Such metabolic sequelae are known to cause renal insufficiency, cardiac arrhythmias, seizures, and death.

The increased rate of cell turnover associated with proliferative disorders and chemotherapy induced cell turnover may result in an increased rate of urate nephropathy and nephrolithiasis (2). This results from the rapid release of intracellular macromolecules that are metabolized to phosphorous and uric acid at a pace that may exceed the patient's clearance capacity. The hyperphosphatemia may result in precipitation of calcium phosphate crystals and lead to increased nephrolithiasis (3). Lastly, hyperuricemia may lead to increased nephrolithiasis via intrarenal precipitation (4).

Lymphoproliferative disorders are a set of diseases characterized by the abnormal proliferation of lymphocytes into a monoclonal population, and include a wide spectrum of diagnostic entities (e.g., follicular lymphoma, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, lymphomas, multiple myeloma, and Waldenstrom's macroglobulinemia). Myeloproliferative disorders are bone marrow stem cell disorders and include chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis, which all have potential to transform into acute leukemias.

While it is well established that lymphoproliferative/myeloproliferative disorders and tumor lysis can result in hyperuricosuria and hyperuricemia, there is limited literature describing the incidence of nephrolithiasis in this select population. There are case reports documenting nephrolithiasis among patients receiving chemotherapy for these disorders (5-7), and a single study examined a larger cohort (5). Moreover, risk factors for nephrolithiasis in patients undergoing chemotherapy have been identified in the pediatric literature but not in an adult chemotherapy population (8). We therefore sought to identify the incidence and risk factors of de novo nephrolithiasis after chemotherapy in adult patients with lymphoproliferative or myeloproliferative disorders.

MATERIALS AND METHODS

With Institutional Review Board approval, patients with lymphoproliferative or myeloproliferative disorders who received chemotherapy were identified through a retrospective view of the institution's electronic pharmacy and medical records (June 2001 through November 2011) at the University of California San Diego (UCSD) Health System. Searching for specific chemotherapy regimens in the UCSD Siemens and PCSi electronic pharmacy records, we identified patients with hematologic malignancies. The Siemens and PCSi retail pharmacy systems recorded each patient's name, medical record number, start and stop date of chemotherapy, chemotherapy regimen, and location of therapy (outpatient infusion center versus inpatient chemotherapy ward). The UCSD Siemens and PCSi electronic pharmacy database was searched for all chemotherapy regimens for all lymphoproliferative and myeloproliferative disorders treated during this time period (See Appendix 1 for a summary of these chemotherapy regimens).

After including all possible chemotherapy regimens in our query, 2,540 patients were identified. Each medical record was independently reviewed using the Epic medical record system (Verona, Wisconsin) to confirm that each of these patients indeed had a lymphoproliferative or myeloproliferative disorder. After reviewing each medical record and excluding patients who either did not have a hematologic malignancy or who already had a diagnosis of nephrolithiasis, we determined the population at risk to be 1,316 patients.

One hundred percent of patients included underwent CT abdomen/pelvis with IV contrast studies before and after chemotherapy. Patients were followed for up to 10 years with CT abdomen/pelvis with IV contrast studies after their last chemotherapy treatment to calculate incidence. We did not rely on patient's history, but reviewed each CT scan independently and confirmed our review with a radiologist's dictation. Each CT abdomen/pelvis was independently reviewed by the same physician.

A prior history of nephrolithiasis was determined by a comprehensive chart review of each

patient's past medical as well as past surgical history. Each note dictated by the patient's oncologist and by their primary care physician was carefully reviewed to assess for prior history of nephrolithiasis. Furthermore, each pretreatment CT study was reviewed to search for history of nephrolithiasis.

Exhaustive manual chart reviews for diagnosis and surgery of nephrolithiasis was performed using Epic to further identify patients with symptomatic stones. All results were confirmed by identifying the stone manually on imaging (abdominal/pelvic computerized tomography (CT). We excluded any subject with a history of nephrolithiasis prior to chemotherapy initiation to determine the primary outcome, cumulative incidence of de novo kidney stone formation. This was not reported as person--time incidence rate because this measure assumes that the incidence rate is constant over different periods of time.

The secondary outcomes were risk factors for stone formation (expressed as odds ratio with 95% confidence intervals) derived from demographic and clinical variables. Clinical variables examined included age, race, gender, primary malignancy, diabetes mellitus, hypertension, hyperlipidemia, obesity, allopurinol use, other stone preventing drugs (potassium citrate, thiazide diuretics), peak serum values (uric acid, calcium, potassium, and phosphorous) and trough urinary pH during chemotherapy. Chemotherapy regimen was not included as a clinical predictor variable because many patients were treated with multiple chemotherapy regimens as a result of relapse, making comparisons difficult. Results of 24-hour urine collections, time to stone formation, size, location, Hounsfield Units (HU) of stone, symptoms of stone presentation, and management of symptomatic stones were also recorded.

Because allopurinol use was more commonly associated with stone formers in our initial analysis, we performed a sub-analysis to determine differences in allopurinol users versus non--allopurinol users.

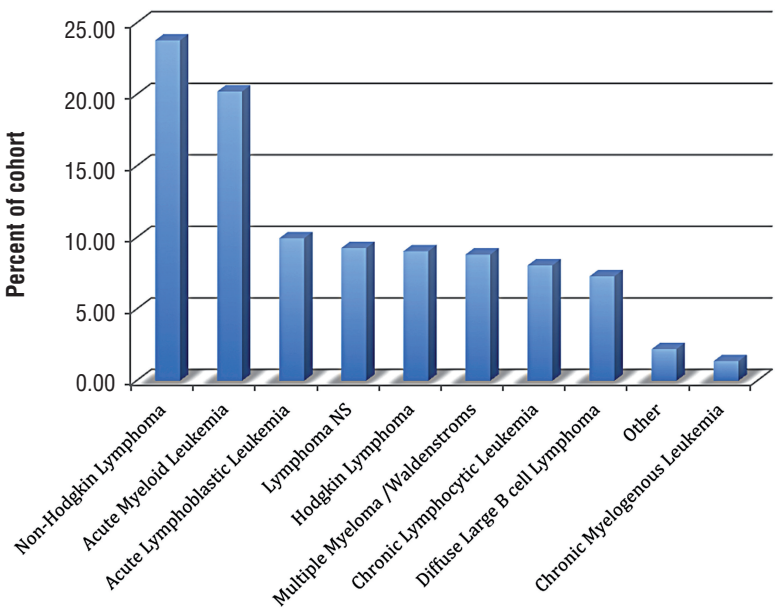
Statistical analysis

Comparative statistics were used to compare demographic and disease specific variables for patients who developed de novo stones versus those who did not, and to compare patients who took allopurinol versus those who did not. Independent t-test and Mann-Whitney U test were used for continuous variables depending on distribution, and Chi-square and Fishers exact test were used for categorical variables. Proportion of all predictor variables forming stones was determined with Chi-square testing for significance. Multivariate analysis using binary logistic regression (with backwards log-rank model building) was performed on variables found to be statistically significant on univariate analysis, or of clinical interest to identify predictors of de novo stone formation; only the variables that remained significant on multivariate analysis were included in the final model. All reported p-values were 2-sided, with $p<0.05$ considered statistically significant. Statistical analyses were performed using SPSS software (version 18.0, SPSS Inc., Chicago IL).

RESULTS

There were 1,316 patients with either a lymphoproliferative or myeloproliferative disorder and no pre-existing stone disease treated between 2001 and 2011. The incidence of overall and symptomatic de novo nephrolithiasis was 72/1316 (5.5%) and 24/1316(1.8%). Lymphoproliferative disorders comprised 68.3% of the cohort, with the most prevalent disorders being Non-Hodgkin lymphoma and ALL, while acute myeloid leukemia (AML) was the most prevalent myeloproliferative disorder (Figure-1). There were no differences in age, gender, race, rates of obesity, allopurinol utilization, urinary pH, and serum phosphorus levels between stone formers and non-stone formers (Table-1). Proportion of patients with diabetes mellitus (13.9% vs. 3%, $p<0.001$), hypertension (20.8% vs. 8.8%, $p=0.003$), hyperlipidemia (15.3% vs. 3.7%, $p<0.001$), stone prevention drug use (26.4% vs. 6.8%, $p<0.001$), hyperuricemia (36.5% vs. 19.7%, $p=0.007$), and hypercalcemia (26.1% vs. 12.9%, $p=0.006$) were statistically higher in the stone-formers. Non-Hodgkin lymphoma constituted 28% of the hematologic malignancies observed in stone formers followed by Hodgkin lymphoma (15%), diffuse large B cell lymphoma (13%) and then AML (13%) (Table-2). There were no differences in

Figure 1 - Proportion of hematologic malignancies observed in cohort, n=1316.



the proportion of primary hematologic malignancies observed in stone formers vs. non-stone formers (p=0.601) (Table-2). Specifically, there were no significant differences in rates of any lymphoproliferative disorder (diffuse large B cell lymphoma, Non-Hodgkins lymphoma, Hodgkins lymphoma, chronic lymphocytic leukemia, acute lymphoblastic leukemia, or multiple myeloma/Waldenstrom's macroglobulinemia) among patients with or without stones, nor were there any significant differences observed in rates of any myeloproliferative disorder (AML or chronic myelogenous leukemia) among patients with or without stones.

Among stone formers, the median urinary pH was 5.5, the mean serum uric acid was 7.5, calcium was 9.6, potassium was 4.3, and phosphorus level was 3.8 mg/dL. Median stone size was 3 mm, median HU was 341, median time from initial chemotherapy to incident stone formation was 3.9 months (1.3-10.7), and 34.8% of stones were symptomatic.

Only 30 of the 72 stone formers (43.5%) underwent very elementary 24-hour urine collections, and median 24-hour urinary volume was 1,873 mL. Only 1 of 30 patients undergoing 24-hour urine collection had 24-hour urinary uric acid and calcium levels analyzed, and this patient had both hyperuricosuria (urinary uric acid 825 mg) and hypercalciuria (urinary calcium 334 mg). No stones were analyzed, however, spot urinalyses performed during chemotherapy demonstrated crystalluria in 11 patients (15.2%): calcium oxalate crystals observed in 10 (14.3%) and uric acid crystals observed in 1(1.4%).

Allopurinol users had different metabolic parameters compared with non-allopurinol users (mean uric acid 7.4 vs. 5.9 mg/dL, p<0.001, mean potassium 4.3 vs. 4.1 mg/dL, p=0.002, and mean phosphorus 4.0 vs. 3.7 mg/dL, p=0.018 respectively). The proportions of diffuse large B cell lymphoma (DLBCL) (11%vs. 6.6%, p=0.020) and CLL (19.2% vs. 5.8%, p<0.001) were also significantly higher in allopurinol users, while proportions of Hodgkin lymphoma (HL) (5.0% vs. 9.9%, p=0.020) and acute myeloid leukemia (AML) (14.2% vs. 21.4%, p=0.016) were significantly lower. Hyperuricemia (35% versus 16.1%, p<0.001, respectively), and hypercalcemia (17.6% vs. 12.8%, p=0.065) were observed more frequently in allopurinol users than non-allopurinol users.

In multivariate analysis, diabetes mellitus (OR=6.38, p<0.001), hyperuricemia (OR=2.31,

Table 1 - Demographics and clinical variables of stone formers and non-stone formers.

	Stones		
	No	Yes	p-value
	(n=1,244)	(n=72)	
Mean Age ± SD, years	51 ± 15.7	52 ± 15.2	0.508
Gender			0.454
Male	765 (61.5%)	48 (66.7%)	
Female	479 (38.5%)	24 (33.3%)	
Race/Ethnicity			0.459
Caucasian	515 (57.0%)	31 (63.3%)	
Other	389 (43.0%)	18 (36.7%)	
Diabetes Mellitus	37 (3.0%)	10 (13.9%)	**<0.001***
HTN	110 (8.8%)	15 (20.8%)	**0.003***
Obesity	8 (0.6%)	1 (1.4%)	0.398
HL	46 (3.7%)	11 (15.3%)	**<0.001***
Malignancy			0.601
Myeloproliferative	385 (31.2%)	20 (27.8%)	
Lymphoproliferative	848 (68.8%)	52 (72.2%)	
Stone Location			-
Kidney	-	63 (91.3%)	
Ureter	-	6 (8.7%)	
Median Stone Size (IQR), mm	-	3.0 (2.0-5.0)	-
Median (IQR) Hounsfield Units (HU) of Stone		341 (254-582)	
Median time from Initial chemo to stone (IQR), months	-	3.9 (1.3-10.7)	-
Median time from Immediate prior chemo to stone (IQR), months	-	1.2 (0.4-4.0)	-
Symptomatic	-	24 (34.8%)	-
Median time from Initial chemo to stone (IQR), months	-	2.5 (0.6-15.4)	-
Median time from Immediate prior chemo to stone (IQR), months	-	1.2 (0.3-8.7)	-
Surgery	-	8 (11.6%)	-
Allopurinol	201 (16.2%)	18 (25.0%)	0.071
Stone Preventing Drug (not including Allopurinol)	84 (6.8%)	19 (26.4%)	**<0.001***
24 hour Urine	-	30 (43.5%)	-
Median 24 hour urine volume (IQR), mL	-	1873 (1225-3565)	-
Median Urine pH (IQR)	5.5 (5.0-6.0)	5.5 (5.0-6.0)	0.296
Urine pH			0.683
<5.5	339 (42.3%)	27 (45.8%)	
≥5.5	463 (57.7%)	32 (54.2%)	
Mean Serum Uric Acid ± SD	6.2 ± 3.0	7.5 ± 3.6	**0.013***
Serum Uric Acid (Reference range 3.4-7.0 ng/dL)			0.007*
<8	519 (80.3%)	33 (63.5%)	
≥8	127 (19.7%)	19 (36.5%)	
Mean Serum Calcium ± SD	9.1 ± 0.9	9.6 ± 1.5	**<0.001***
Serum Calcium (Reference range 8.6 -10.5 ng/dL)			0.006*
<10	1051 (87.1%)	51 (73.9%)	
≥10	156 (12.9%)	18 (26.1%)	
Mean Serum Potassium ± SD (Reference range 3.5-5.1 mmol/L)	4.1 ± 0.6	4.3 ± 0.6	**0.039***
Mean Serum Phosphorous ± SD (Reference range 2.7-4.5 ng/dL)	3.8 ± 1.2	3.8 ± 1.0	0.771
Deceased	146 (11.7%)	9 (12.5%)	0.850

Table 2 - Rates of primary malignancy in stone formers vs. non-stone formers.

	Stones		
	No	Yes	p-value
	(n=1,244)	(n=72)	
Lymphoproliferative Disorders	947 (76.1%)	56 (77.8%)	0.601
Diffuse Large B cell Lymphoma (DLBL)	87 (7%)	9 (12.5%)	0.098
Non-Hodgkin Lymphoma (NHL)	293 (23.6%)	20 (27.8%)	0.396
Hodgkin Lymphoma (HL)	108 (8.7%)	11 (15.3%)	0.086
Lymphoma NS	120 (9.6%)	2 (2.8%)	0.057
Chronic Lymphocytic Leukemia (CLL)	100 (8%)	6 (8.3%)	0.826
Acute Lymphoblastic Leukemia (ALL)	127 (10.2%)	4 (5.6%)	0.308
Multiple Myeloma (MM)/Waldenstroms	112 (9%)	4 (5.6%)	0.397
Myeloproliferative Disorders	274 (22%)	10 (13.9%)	0.601
Acute Myeloid Leukemia (AML)	257 (20.7%)	9 (12.5%)	0.099
Chronic Myelogenous Leukemia (CML)	17 (1.4%)	1 (1.4%)	1.000
Other	23 (1.8%)	6 (8.3%)	**0.003***

Other: T-cell prolymphocytic leukemia, Aplastic anemia, chronic congenital neutropenia, CVID
HIV with Autoimmune hemolytic anemia, idiopathic hypogammaglobulinemia, leukemia, Myelodysplastic syndrome, Myelofibrosis, myeloid sarcoma, Pancytopenia, r/o MDS, plasma cell leukemia, Polycythemia Vera, t-cell leukemia

p=0.007), and hypercalcemia (OR=2.14, p=0.022) at time of chemotherapy predicted de novo stone.

DISCUSSION

The findings from this study spanning 10 years support the hypothesis that metabolic derangements during chemotherapy are associated with an increased risk of nephrolithiasis. Previous extensive reports demonstrating this include a pediatric study of over 2,000 children treated for ALL and a Korean study of over 900 adults who were treated for both lymphoproliferative and myeloproliferative disorders (5,8). Both investigations demonstrated that the incidence of nephrolithiasis in these populations was significantly higher than in the general population. Until these reports, the claim of increased nephrolithiasis risk with hematologic malignancy had been substantiated by only case reports and the plausible pathophysiologic theory of endogenous nucleotide catabolism.

The investigators of the pediatric stone study postulated that stone formation was associated with chemotherapy, but perhaps more importantly was due to glucocorticoid therapy. Steroids are used in multiple contexts for lymphoproliferative diseases and can increase the risk of nephrolithiasis by decreasing renal calcium absorption. The authors cited the predominance of calcium-based stones as opposed to uric acid stones as evidence supporting the steroid-nephrolithiasis hypothesis (8). However, almost half of stone analyses in the Korean adult study showed uric acid stones despite the common use of glucocorticoid therapy (5).

Our study included a predominance of calcium oxalate over uric acid crystals, although no stones were formally analyzed, and the median HU of de novo stones was 341, suggesting a mixture of

both calcium and uric acid stone compositions (9). These findings are consistent with our analysis of nephrolithiasis risk factors, which demonstrated in multivariate analysis that diabetes mellitus, hyperuricemia, or hypercalcemia significantly increased risk of nephrolithiasis. The presence of hypercalcemia and hyperuricemia permits heterogeneous nucleation and subsequent calcium stone formation (10). Diabetes is thought to be a risk factor for uric acid calculi due to insulin resistance leading to low urinary pH associated with defective ammonia synthesis occurring in the proximal tubule cell as well as ammonium transport into the renal tubular lumen (11). The role of diabetes mellitus in our study is significant, as it was associated with an over 6-fold increased risk of nephrolithiasis. Allopurinol is a xanthine oxidase inhibitor frequently used prophylactically to decrease the uric acid production prior to instituting chemotherapy for patients at risk for TLS (12). In a double blinded randomized prospective trial, allopurinol utilization decreased the number of stone events while increasing the time to recurrence of stone event among calcium oxalate stone formers with hyperuricosuria on 24-hour urine collections, substantiating its preventive role in patients at risk for calcium oxalate nephrolithiasis (13). Published guidelines regarding the prevention and management of TLS include specific recommendations for the appropriate utilization of allopurinol (14). Risk factors for TLS include tumor type (Burkitt's lymphoma, lymphoblastic lymphoma, diffuse large cell lymphoma, ALL), tumor burden/extent of disease defined by elevated WBC>25,000 and/or bulky nodal disease >10 cm, preexisting renal failure, and baseline uric acid≥7.5 mg/dL (14).

These high-risk patients are recommended to undergo aggressive hydration, urinary alkalinization, diuresis, and allopurinol or recombinant urate oxidase (rasburicase) prophylaxis. Our data demonstrated patients at higher risk for TLS received allopurinol more frequently than those at lower risk, as one would expect, but in multivariate analysis use of allopurinol did not decrease incident stone risk, presumably due to selection bias. Given this and our finding that hyperuricemia is a risk factor for stone formation in this population, recombinant urate oxidase (rasburicase) may offer an advantage, as it catalyzes the conversion of uric acid to allantoin, which is 5-10 times more soluble in urine (14). Rasburicase has been well studied in both pediatric and adult patient populations at risk for TLS, demonstrating a significantly more rapid lowering of serum uric acid levels compared to allopurinol (15-17). Current guidelines for management of TLS recommend rasburicase in pediatric patients at high risk for TLS and in adults with hyperuricemia diagnosed with TLS or refractory to allopurinol (14). Our findings suggest that prompt and effective treatment of hyperuricemia may prevent upper tract stone formation and reduce the incidence of nephrolithiasis.

Unfortunately, our study highlights both the low number of 24-hour urine collections (43.5%) as well as the lack of necessary detail in these 24-hour urine collections (3.33%) performed in high-risk stone formers. Urological consultations were infrequently obtained in this patient population, and as such, metabolic stone evaluations were rarely performed in these patients. While it would have been incredibly useful to have a 24-hour urine collection in every single stone former, the absence of this data provides an area of opportunity for urologists to improve the care of these patients. Urologists should be consulted in the care of such patients to appropriately work up the etiology of stone disease, and thereby prevent future stones from occurring.

Inherent limitations of this retrospective study are acknowledged, specifically, selection bias was observed when comparing patients receiving allopurinol prophylaxis. Patients in our study attended regular office visits and underwent frequent cross-sectional imaging for oncologic management and surveillance, resulting in more opportunities to diagnose asymptomatic nephrolithiasis. Moreover, patients may have been more likely to report symptoms of abdominal or flank pain at follow-up visits, increasing the likelihood of diagnosis of nephrolithiasis.

CONCLUSIONS

We report the incidence of de novo nephrolithiasis in patients with lymphoproliferative or myeloproliferative disorders undergoing chemotherapy. This study also identifies diabetes

mellitus, as well as hyperuricemia and hypercalcemia at time of chemotherapy as risk factors for nephrolithiasis that should assist oncologists in appropriately selecting patients for prophylaxis, while also providing urologists an earlier opportunity to collaborate and assist in treatment and evaluation of nephrolithiasis.

ABBREVIATIONS

ALL = Acute Lymphoblastic Leukemia
AML = Acute Myeloid Leukemia
CLL = Chronic Lymphocytic Leukemia
DLBL = Diffuse Large B cell Lymphoma
HL = Hodgkins lymphoma
HU = Hounsfield Unit
MM = Multiple Myeloma
NHL = Non Hodgkins Lymphoma
TLS = Tumor lysis syndrome

CONFLICT OF INTEREST

None declared.

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APPENDIX 1: LIST OF CHEMOTHERAPY REGIMENS

Lymphoma

1. Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with/without rituximab
2. Etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide (EPOCH) with/without rituximab
3. Ifosfamide, carboplatin, and etoposide (ICE) with or without rituximab
4. Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)
5. Nitrogen mustard, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, and prednisone (Stanford V)

Acute myelogenous leukemia

1. Cytarabine and idarubicin or daunorubicin (7+3)
2. Fludarabine, cytarabine, idarubicin, and filgrastim (FLAG)
3. All trans-retinoic acid (ATRA)
4. Chronic myelogenous leukemia
5. Imatinib, dasatinib and nilotinib

ORIGINAL ARTICLE

Vol. 40 (6): 781-789, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.09

A transobturator adjustable system for male incontinence: 30–month follow–up of a multicenter study

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ABSTRACT

Purpose: To report long-term results of the Argus T adjustable system for treatment of post-prostatectomy urinary incontinence (PPI).

Materials and Methods: From October 2007 to August 2008, 37 patients with PPI were included in a prospective, single-arm, multicenter trial of treatment with the Argus T adjustable system (Promedon, Argentina). Preoperative evaluation included urine culture, urethrocystoscopy, urodynamic testing, 24-h pad weight test (PWT) and quality of life questionnaires. Patients were stratified according to baseline degree of incontinence (mild–moderate or severe). Postoperative evaluation included immediate PWT, quality of life questionnaires and daily use of pads at 1, 12 and 30 months.

Results and Conclusions: One patient was lost to follow-up. At the 30-month follow--up, 24/31 patients (77%) were dry, 3/31 (10%) improved and 4/31 (13%) were failures. In particular, in the mild-moderate group, 8/8 (100%) patients were dry. In the severe group, 20/28 patients (71%) were dry, 3/28 (11%) improved and 5/28 (18%) were failures. Median visual analogue scale (VAS) scores dropped from 9 (4-10) to 0.5 (0-10) and International Consultation on Incontinence Questionnaire Short Form scores from (ICIQ-SF) 19 (12–21) to 1 (0–10). Retrograde leak point pressure increased from 18 (5–29) to 35 (22–45) cm H_2O after intraoperative adjustment. Complications included immediate postoperative infection in 2/36 patients (6%) and transient inguinal and/or perineal pain in 22/36 patients (61%). Argus T has a long-term high success rate (86% cure + improvement at the 30-month follow-up). Good outcomes were achieved even in severe incontinence cases and maintained for over 30 months.

ARTICLE INFO

Key words:
Suburethral Slings; Prostatectomy; Urinary Incontinence; Urodynamics

Int Braz J Urol. 2014; 40: 781-9

Submitted for publication:
October 19, 2013

Accepted after revision:
March 03, 2014

INTRODUCTION

Although rare, stress urinary incontinence secondary to prostate surgery, whether for prostate cancer or benign prostatic hyperplasia (BPH), causes significant deterioration of patients' quality of life. Persistent urinary incontinence occurs in 5–10% of post radical prostatectomy patients and in 0.5–3% of post BPH surgery patients. In both situations, incontinence can be severe enough to require surgical management.

Conservative management is generally recommended during the first 6–12 months after prostatectomy. Behavioral modifications, pelvic floor muscle training and drug therapy have been the most frequently recommended options.

Surgical interventions are the next treatment option for persistent UI. Peri-urethral injection for temporary relief, minimally invasive compression devices, fixed and adjustable slings and artificial urinary sphincters (AUS) are the current recommended forms of surgical treatment (1-3).

Suprapubic slings had seldom been used prior to Schaeffer et al. report in the late 1990s of a success rate of 75% (cure + improvement) for a bulbourethral device in a group of 64 patients with a 2-year follow-up (4). After this initial report, several other researchers assessed this procedure and added modifications to the original design. Romano et al. (2) reported a success rate of 83% (73% cure + 10% improved) for an adjustable bulbourethral device inserted via a suprapubic approach in a group of 48 patients with a mean follow-up of 7.5 months. The same group later reported long-term stability with a 78.8% success rate (66.0% cure + 12.8% improved) after a mean follow-up of 45 months (5).

To find a simpler and safer approach for implantation, we evaluated a transobturator approach in 2003 (6). After proving its feasibility in 2007, we began a multicenter trial. Data from this study are reported in this paper.

MATERIALS AND METHODS

Potential subjects were screened for a prospective, single-arm, multicenter trial from October 2007 to August 2008. The study protocol was approved by the corresponding independent ethics committees and written informed consents were obtained before patients' inclusion. A group of 37 patients who met the eligibility criteria were finally selected. Inclusion criteria were 1 year or more of PPI (of any degree of severity) that had altered quality of life to the extent that the patient agreed to a surgical procedure and urodynamic confirmation of stress incontinence. Exclusion criteria included untreated urinary infection, urethral stricture, low bladder capacity (less than 200mL) and bladder stone unable to be resolved during a sling procedure.

Preoperative evaluation included a complete urologic exam, urine culture, urethrocystoscopy, 24-h PWT and quality of life questionnaires (ICIQ-SF and VAS). Urodynamic testing was also performed to assess the filling variables of sensitivity, capacity, compliance, detrusor overactivity and to confirm the stress nature of the UI as well as the retrograde leak point pressure (RLPP) (7, 8). The emptying variables of free flow and voluntary detrusor contractility were also recorded. The baseline characteristics of the enrolled patients are shown in Table-1.

Patients were grouped according to their degree of incontinence into mild–moderate and severe categories. This stratification was based on 24-h PWT preoperative measurements. The patient was assessed as having mild–moderate incontinence if the leakage was less than or equal to 400g and severe incontinence if it was greater than 400g (9) (Table-1).

An amendment was made to the protocol in four of the five initial centers to include a follow-up at 30 months. For this reason, 31 patients were followed at 1, 12 and 30 months and the remaining five patients only at 1 and 12 months postoperatively.

Argus T adjustable systems (Promedon, Argentina) were surgically implanted in the patients. This system consists of two cone columns that serve as fixation arms and a central pad made of radiopaque silicone foam. The system is completed by placing two rings (washers) on each fixation arm to provide safe anchoring and positioning of the device against the fibro muscular tissue of the obturator foramen.

The surgical procedure is as follows. The patient is placed in the lithotomy position, under spinal or general anesthesia. As has previously been described (2, 5, 10), a perineal incision is performed in the same way as for suprapubic or transobturatory devices to dissect the bulbar urethra at the level of the inter bulbospongiosus and ischiocavernous muscles area. The bulbospongiosus muscles are left in situ and the urethra is not mobilized from the central tendon. A helical needle is then introduced via the inguinal fold, 2cm below the insertion of the adductor magnus muscle, using an outside-in approach such that the needle tip appears in the dissected area of the perineum. The fixation arm is pulled out along the needle path and the procedure repeated on the other

Table 1 - Patients' baseline characteristics.

Characteristic	N (%)	Median (range)
Age (years)		70 (58–81)
RLPP (cmH_2O)		18 (5–29)
Underlying pathology		
Post-prostate cancer	30 (81)	
Post-adenomectomy	7 (19)	
Adjuvant Radiotherapy	2 (5)	
Prior incontinence surgery	6 (16)	
Argus (retropubic)	1 (3)	
ProACT™ (parurethral balloon)	3 (8)	
Macroplastique™ (injectable bulking agent)	2 (5)	
Degree of incontinence		24-h PWT (g)
Mild–moderate	8 (22)	215 (100–350)
Severe	29 (78)	1200 (500–2880)
Total	**37 (100)**	**1100 (100–2880)**

side. After placing the rings on the fixation arms and checking that the foam pad is centered, symmetrical adjustment is performed one cone at a time until an RLPP of 30 to 40cmH_2O is achieved. The ruler (included in the kit) must be positioned with the 0 (zero) at the level of the patient's pubis (Figures 1-4).

The urethral catheter is left in place for 24 to 48 h. Patients are given intraoperative cephalosporin 1g and gentamicin 80mg every 12h until the catheter has been removed, after which oral ciprofloxacin (500mg every 12h) is prescribed for 7–10 days.

The follow-up plan included evaluations at 1, 12 and 30 months. Quality of life was assessed by the ICIQ-SF questionnaire and a VAS scale (from 0 [no discomfort] to 10 [very uncomfortable]). The degree of incontinence was objectively assessed on the basis of 24-h PWT at the first postoperative follow-up visit (1 month) and by daily pad use on the other visits.

Figure 1 - ARGUS T adjustable system – Promedon SA.

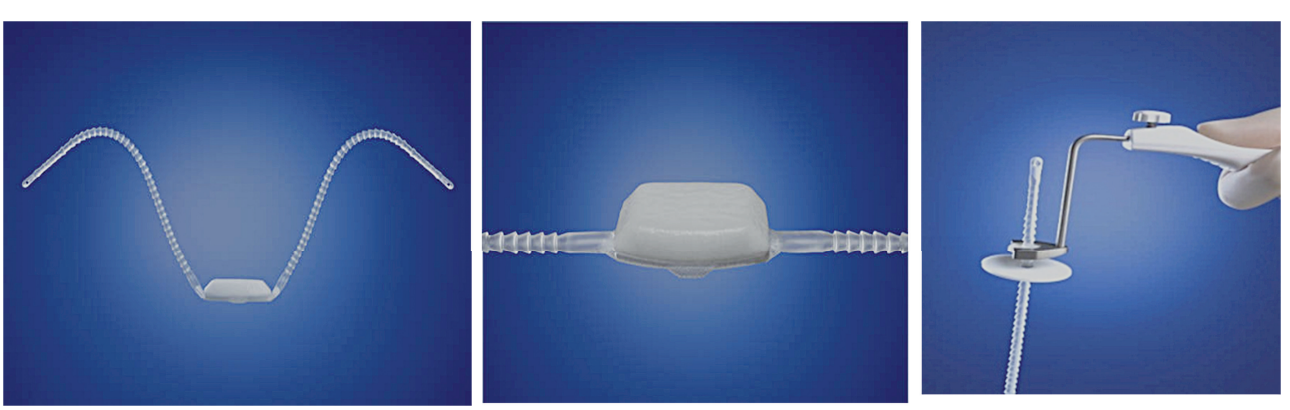


Figure 2 - Left - tip of left needle in the perineal wound. Right – Implant: Pad, Rings and hidden fixation arms, in final position after the RLPP measure.

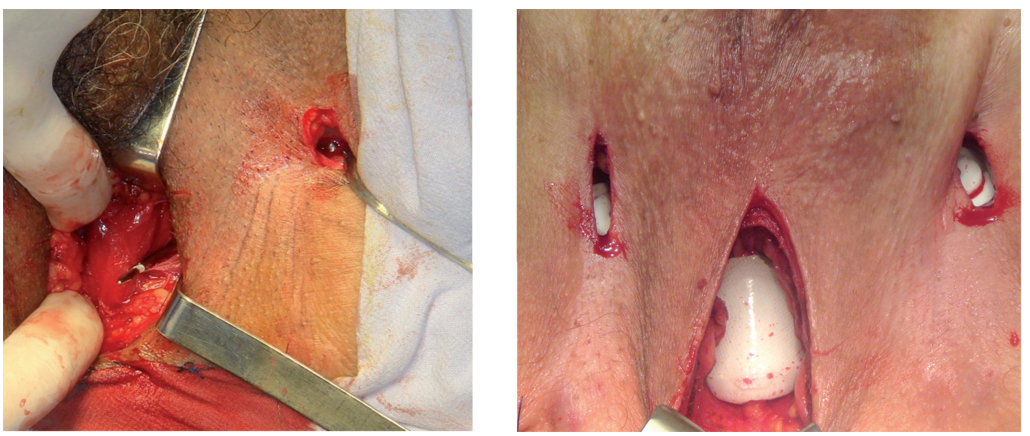


Figure 3 - Left – urethral lumen before the procedure. Right – urethral lumen after RLPP adjust.

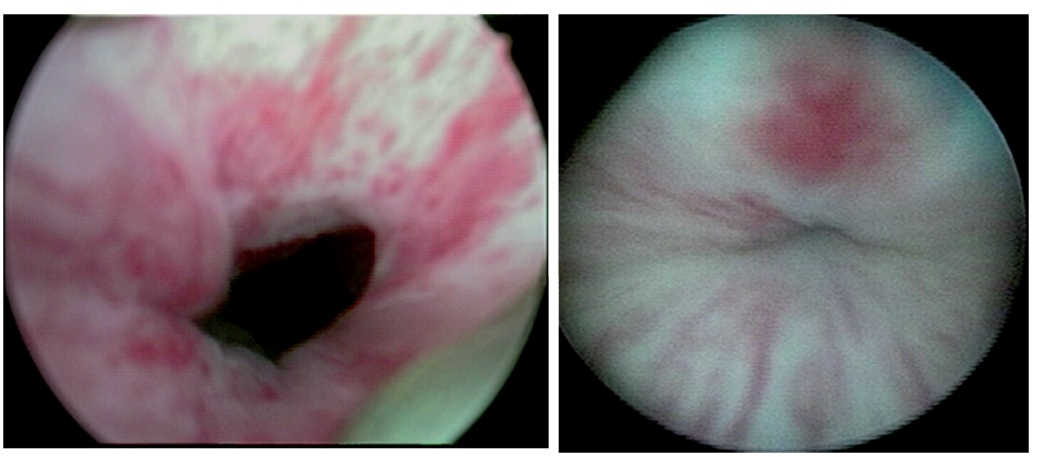
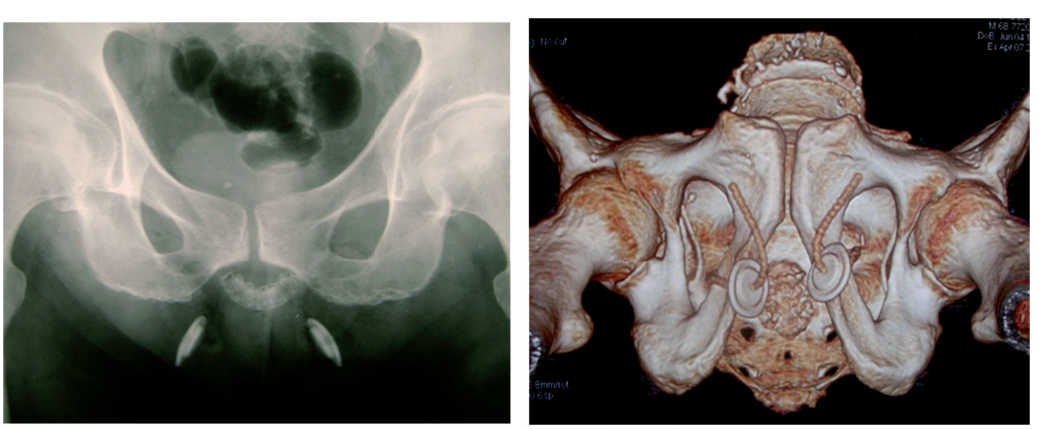


Figure 4 - Left – final position of the implant in a plain x-ray. Right – final position of the implant in a MRI 3D reconstruction.



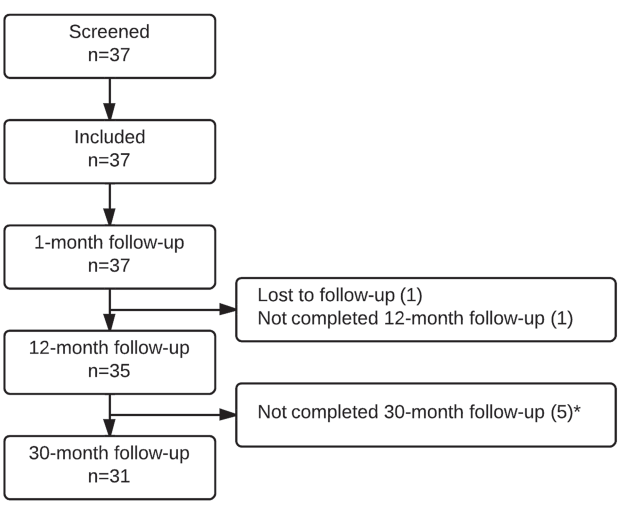
The patients' statuses were classified according to the daily use of pads as dry (no pads or one for protection), improved (one wet pad a day) or failure (two or more wet pads daily or implant removal).

During follow-up, adverse events were also recorded and the Clavien–Dindo Classification of Surgical Complications was used to report them (11, 12).

RESULTS

One of the 37 study patients was lost to follow-up after the first postoperative visit. As has already been stated, five patients were only followed up for 12-months. The study subject distribution tree is shown in Figure-5.

Figure 5 - Study subjects' distribution tree.



*The five patients who did not complete the 30-month follow-up were from the center that did not amend the protocol to extend the duration of follow-up.

In the short term, at the 1-month follow-up the median 24-h PWT had improved from 1100g (100–2880g) overall to 0g (0–35g) in dry patients and 50g (50–72g) in improved patients. The RLPP measured during the process of surgical adjustment of the implant increased from 17 (5–29) to 35 (22–45)cmH_2O.

All quality of life indicators changed favorably: the median VAS score from 9 (4–10) to 0.5 (0–10) and the ICIQ-SF from 19 (12–21) to 1 (0–10) (Table-2).

In the mild–moderate group, all eight patients achieved continence. In the severe group 20/28 patients achieved continence and 3/28 patients improved, requiring only one pad per day (Table-3).

No one in the mild–moderate group needed postoperative readjustment because they all achieved continence postoperatively. In the severe group, seven patients (25%) who remained incontinent after surgery gave their consent to readjustment. The median time from the initial surgery to readjustment was 14 (7–25) months. Results of readjustment are reported in Table-4.

Immediate infection occurred in 2/36 patients (5.6%). One of them required implant removal (Grade III-a). This patient had previously had a ProACT™ (Uromedica, USA) implanted; this had also required removal because of infection. The other patient with immediate infection was treated with local wound care and antibiotics and required no further intervention after 3 months (Grade II). Upon catheter removal, postoperative urinary retention occurred in 2/36 patients (5.6%). In one of these patients, the retention was overcome by postoperative readjustment (loosening) of

Table 2 - Postoperative results.

		Pre-op	1 month	12 months	30 months
Daily pad use N (%)	Dry		26 (70)	28 (80)	24 (77)
	Improved		6 (16)	3 (9)	3 (10)
	Failed		5 (14)	4 (11)	4 (13)
ICIQ-SF score median (range)		19 (12–21)	2 (0–20)	2 (0–20)	1 (0–10)
VAS score median (range)		9 (4–10)	1 (0–10)	0 (0–10)	0.5 (0–10)

Table 3 - Results segregated by baseline degree of incontinence, according to each patient's last follow-up.

Baseline degree of incontinence	Postoperative outcome	
Mild-moderate	Dry	8/8 (100%)
	Improved	0/8 (0%)
	Failed	0/8 (0%)
Severe	Dry	20/28 (71%)
	Improved	3/28 (11%)
	Failed	5/28 (18%)

Table 4 - Readjustment of the Argus T device postoperatively.

Patient group	Number of readjustments	Outcome after readjustment	
Mild–moderate	0/8 (0%)	NA	
Severe	7/28 (25%)	Dry	5/7 (72%)
		Improved	1/7 (14%)
		Failed	1/7 (14%)

the implant, thus decreasing the RLPP (Grade III-a). The other patient had impaired bladder contractions (hypocontractility) postoperatively: after 6 months of intermittent catheterization, he regained spontaneous bladder evacuation with no post-voiding residual urine (Grade II).

Transient inguinal and/or perineal pain was reported immediately after surgery by 22/37 patients (61%). The pain resolved within 3–4 weeks after treatment with analgesics, nonsteroidal anti-inflammatory drugs (Grade I) and/or corticosteroids (Grade II). In one patient (2.8%), pain persisted for 2 months before resolution.

DISCUSSION

As recently as 10 years ago, the only reliable surgical treatment for PPI was the AUS (13, 14). Although it has been associated with significant complications such as infection, erosion and mechanical failure, including urethral atrophy with recurrent incontinence, and a revision rate of greater than 50% (15, 16), this procedure continues to play a predominant role.

During the last decade, a series of adjustable and non-adjustable devices have been developed for treating PPI. All of them attempt to achieve continence by urethral coaptation, rather than by closing the urethral lumen as the AUS does. The latter works as a hydraulically operated open-close valve that produces either complete obstruction of the urethral lumen or complete opening, whereas the coaptation devices aim to increase the baseline RLPP to reinforce the sphincteric mechanism. Therefore, with coaptation devices continence and micturition are ruled by the normal physiological balance between intravesical pressure and urethral resistance. Adjustable devices offer a great advantage over the non-adjustable ones: their ability to be adapted to changes in patients' conditions. Examples of adaptable devices are the Argus (Promedon, Argentina), Remeex (Neomedic, Spain), ATOMS (A.M.I., Austria) and ProACT™ (Uromedica, USA) devices (5, 17-20).

Among the non-adjustable devices are various models of autologous facials slings or polypropylene tapes such as Invance™ (bone anchored sling), AdVance™ and other devices (21-27).

The AdVance™, one of the most commonly used non-adjustable devices, reportedly has very good results (around 80%) in selected cases of mild to moderate PPI (3). It is claimed that this retro-urethral transobturatory sling works by repositioning the residual sphincter to an intra-abdominal location by mobilizing the urethra from the perineal central tendon, thus avoiding the urethral hypermobility that can be caused by surgery. At the same time, the urethra is occluded by the sling, which should be implanted under tensioning, as is recommended (25, 26).

The main advantage of adjustable systems is that they allow postoperative increasing or decreasing of sling tension to improve or correct initial outcomes. Sling tension can be increased to augment urethral resistance in patients whose incontinence persists. In addition, sling tension can be decreased by loosening the sling, thus decreasing the RLPP, in patients with urinary retention or obstruction. In this study, five patients who remained incontinent after surgery benefited from this advantage. They achieved continence (dry patients) after postoperative sling adjustments. Furthermore, by loosening the urethral coaptation postoperatively, it was possible to reverse the urinary retention of the patient who had not been able to reverse it naturally. Argus T's adjustment rings provide reliable fixation, which helps to maintain the coaptation achieved during surgery. These rings also offer a point of reference for postoperative tension adjustments.

Soljanik et al. (28) highlighted the need for reducing sling slippage and failure at short-term follow-up in patients with the AdVance™ device. They improved the surgical technique by tunneling the sling arms subcutaneously and using at least four non-absorbable sutures instead of an absorbable one.

It is important to note that, in most patients, the ability to adjust the Argus T to an intraoperative RLPP of 30 to 40cmH_2O, combined with the reliable anchoring supported by the rings, resulted in sustained positive outcomes without the need to perform subsequent adjustments. The recommended RLPP range has been established over more than 10 years of experience, with the aim of applying the minimum pressure in the urethra necessary to achieve continence while minimizing pain, erosion and obstruction (2, 5, 29).

In the mild–moderate incontinence patients, who comprised 22% of study patients, the results obtained were excellent (100% continence). In addition, the patients with severe incontinence (78% of study patients) achieved a success rate of 82% (71% cure + 11% improvement). These figures are encouraging in terms of efficacy and, remarkably, the results are good regardless of the severity of incontinence preoperatively. Some devices that have shown promising results in patients with mild to moderate incontinence, such as the AdVance™, are relatively ineffective in, and therefore not indicated for, patients with severe incontinence (3, 30). Consequently, in severe cases for which options for effective surgical treatment are limited, the Argus T is an attractive alternative, as evidenced by the results presented in this paper.

Infections occurred in our series only during the immediate postoperative period and are therefore seemingly related to intraoperative contamination. However, our infection rates are similar to or even lower than those reported for other implants used for management of male incontinence, such as the AUS and Argus devices, both of which are also made from silicone (5, 16).

In summary, historically bulbourethral compression devices have been a prominent component of the armamentarium for treatment of PPI and have achieved very satisfactory results in 65 to 90% of patients (3, 5, 10, 17, 21, 22, 24, 26, 27). Based on examination of data from medium and long-term follow-up, we believe that the common goal of all these devices is to create mild bulbourethral pressure that allows coaptation of the mucosa, thus controlling incontinence. Indeed, it appears that the lower the passive resistance required to achieve continence, the greater the likelihood of avoiding dysuria, urinary retention, pain and erosion (29).

CONCLUSIONS

We found that the Argus T adjustable system can be easily and safely implanted through a transobturator approach, providing a high success rate (86% cure + improvement). We achieved good

outcomes even in patients with severe incontinence and these were sustained during 30 months of follow-up. This device is a valuable treatment option for most patients with PPI.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 790-801, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.10

One hundred cases of sui treatment that failed: a prospective observational study on the behavior of patients after surgical failure

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ABSTRACT

Objectives: Determine what happens to patients after unsuccessful SUI operations and to explore the reasons why these patients change doctors.
Materials and Methods: One hundred consecutive failed patients treated for SUI were interviewed about the exams requested after persistence of the incontinence as well as the reasons they abandoned their primary doctors through a structured questionnaire.
Results: Among the patients with cases of anterior colporrhaphy, bladder suspensions or slings, 34.3%, 13.7% and 8.3%, respectively, were not offered any further type of investigative procedures to clarify the failure. Urodynamic evaluations were recommended in 75% of failed slings, and 66.6% of the patients proceeded with these tests. In contrast, only 31% of patients with bladder suspensions and 40% of patients with anterior colporrhaphy were recommended for urodynamic investigations, and only 44.4% and 28.5% of them, respectively, proceeded with the option. Patients´ delusions were reinforced by the doctors' attitude toward the investigations. Vacuous justifications and the lack of intention to seek improvement were the driving forces causing the patients to change doctors.
Conclusion: Unsuccessful patients are evaluated in a non-protocol form. Difficulty in clarifying the reasons for surgical failure and the disruption of the doctor-patient relationship are the main reasons why patients abandon them.

ARTICLE INFO

Key words:
Urinary Incontinence; Urodynamics; Female; Urology

Int Braz J Urol. 2014; 40: 790-801

Submitted for publication:
July 22, 2013

Accepted after revision:
May 05, 2014

INTRODUCTION

The treatment failure of urinary incontinence may occur with any specialty physician dealing with irregular or difficult cases (1-4).

The rate at which patients submitted to unsuccessful treatments demand ancillary, novel or repetitive operations depends on the patient's subjective impression of the treatment as a failure. In that context, satisfaction with the results is related to the patient's expectations before the operation and the cultural pressures demanding dryness and bladder control, albeit what may represent a cure to one individual may be taken as an inappropriate result by someone else (5).

The demand for complementary treatments due to unsatisfactory clinical results is also a reflection of the patient´s myriad impressions of the complexity of the final purpose, the invasiveness and the individual discomfort and inconvenience

of repeating a surgery, especially after a failure, leading to a disrupted relationship with the primary attending doctor.

These factors may affect the clinical rate of patients being lost to follow-up in any practice or even in academic trials, although it must be recognized that some patients simply do not return because of a successful clinical result (6,7).

The causes of patients being lost to follow--up and the reasons for not pursuing the self-desired clinical result are poorly reported in the literature. Unraveling the reasons patients change doctors or refuse to proceed to complimentary exams is essential to understand the behavior of unsuccessful treatment. We herein examine the reasons that patients abandon and disbelieve their primary doctors after perceiving the surgical treatment for stress urinary incontinence (SUI) as a failure.

MATERIALS AND METHODS

During a 16-year time period, 118 consecutive patients previously treated elsewhere were referred to our tertiary referral center to evaluate their clinical failure after surgical treatment for SUI at the time the patient reconsidered to continue pursuing treatment for her problem anteriorly abandoned. At the time of the urodynamic investigation patients were prospectively queried with a structured questionnaire (Appendix).

The patients were consecutively enrolled only if the main complaint that led them to have an operation in the past was SUI and if they subjectively felt that the surgical treatment had failed after at least 5 consecutive visits of follow--up. After a pilot study with 18 cases - a development phase in which answers were simulated and analyzed - a structured questionnaire was generated (Appendix). This questionnaire allowed the data collection of the reasons that the patients abandoned their doctors, the investigative exams required or suggested to clarify the causes of failure and the therapeutic options proposed by the surgeon to investigate and correct the clinical failure. A case study was carried out prospectively for 100 consecutive patients. The study was approved by the Internal Ethics Committee at Hospital Beneficência Portuguesa and no informed consent was needed for this investigative purpose. Informed consent was signed for the well-established urodynamic protocol.

Patients were guided through structured and exclusive questions (only one main answer was allowed - Appendix) to clarify the reasons for their dissatisfaction and failure, the reasons they sought a different doctor´s evaluation and their further therapeutic options to improve or correct the surgical failure by the primary doctor when the patient demanded a better clinical result. Similarly, the doctor´s arguments regarding the patients´ perceptions of the doctor´s explanations were also studied, together with the reasons that led the patient to abandon the doctor. Exclusive answers might limit the complex feelings surrounding doctors abandonment but options were defined after an ordinary system with the most common catalogued answers during the development phase.

All of the patients were also questioned by the authors with the help of drawings and graphical materials to help identify the surgical techniques employed to treat the SUI. Their route of surgical access, the presence of any implanted material and the examined scar also helped to distinguish patients. Burch was specifically named as a group, as many doctors mentioned the name during the pre-operative interviews regarding the type of the surgical technique to be employed. However, if another technique was named or could not be precisely determined although an abdominal scar was present, it was grouped as an abdominal bladder suspension.

Patients were grouped into one of 5 surgical groups: the anterior colporrhaphy, Burch, abdominal bladder suspension, TVT or TOT techniques.

Due to its unique nature, the urodynamic investigation was easily recalled by the patients. The patients were closely questioned concerning the intention to perform such an exam for the first time (as not all patients had undergone this exam before the operation) or to repeat the exam after a failure.

Detailed descriptions and illustrations of the urological exams were also shown to easily identify the type of exams requested to investigate the failure by the primary surgeon. Multiple choices were allowed for this latter item.

When possible and the techniques could not be elucidated, the primary doctor was contacted by telephone to address any unanswered questions about the case.

The time the patient realized that from her perspective the operation was a failure was also reported.

The patients were also questioned extensively about the reasons why they did not mention the surgery failure to their primary doctor and the main reason that led them to change their attending doctor.

Finally, the patients were asked if they informed the attending surgeon that they were going to seek another specialist or if the primary doctor recommended them to seek a colleague.

Tables with the patients' answers were constructed. Logistic regression analysis was used when possible, and relationships between the surgical technique and patients´ answers were also analyzed by multivariable logistic regression analysis.

RESULTS

The mean time from when the failed SUI operation was performed until the interview and urodynamic evaluation was determined, and the age of the 100 patients with failed operations is presented in Table-1.

The patients submitted to the anterior colporrhaphy and Burch techniques were older, and they had the longest interval from the failed operation until the urodynamic evaluation. This observation reflected the use of an outdated technique to treat SUI in comparison to more contemporary techniques involving suburethral slings – Table-2.

Among the 100 patients with failed operations, the vast majority (60%) realized the operation failed after only 6 months of follow-up, although 31% could not precisely state the time to failure.

When the patients were asked about the nature of the exams that were recommended to investigate the causes of failures, 38% (14/36) of those submitted to sling procedures had undergone cystoscopy, while 12.5% (4/29) of those submitted to bladder suspension techniques and 11.4% (4/35) of those submitted to anterior colporrhaphy were recommended to undergo this exam. Urodynamic studies were recommended for 75% of the failed sling operations, while 31% of the bladder suspensions and 40% of the anterior colporrhaphy were recommended to undergo this exam.

In the same manner, IVP and UCM accounted for 68% of the requested exams for those patients operated on with anterior colporrhaphy, while only 24% of bladder suspension patients and 38% of sling patients were recommended to undergo these exams.

The urodynamic studies requested by the primary surgeon who operated on the studied population were available in only 26 cases (26%) although 50% of the failed patients were instructed

Table 1 - Demographic characteristics of 100 failed patients surgically treated for SUI.

	N	Age in years (range)	Mean time from the primary failed SUI operation to interview/ urodynamic – in years (range)
Anterior colporraphy	35	65.7 (32-81)	15.5 (0.8 - 27)
Burch	17	54.4 (48-77)	9.7 (4 - 18)
Abdominal suspension	12	53.4 (50-67)	10.6 (6 -15)
TVT	28	47.8 (38-94)*	8.2 (0.6 - 11)
TOT	8	44.3 (38-52)**	3.3 (0.8 - 5)

* - Statiscally significant as compared to Anterior colporraphy, Burch and Abdominal suspension groups
** - Statiscally significant as compared to Anterior colporraphy, Burch and Abdominal suspension groups

Table 2 – Time-frame of patient realizing failure of the operation.

"How long did you take to realize the operation did not work?"

	Anterior colporraphy	Burch	Abdominal suspension	TVT	TOT	Total cases
1 month	20% (7)	35.2% (6)	33.2% (4)	7.1% (2)	12.5% (1)	21%
3 months	8.5% (3)	11.8% (2)	24.9% (3)	25% (7)	12.5% (1)	16%
6 months	17.1% (6)	0	8.3% (1)	46.4% (13)*	50% (4)	23%
9 months	0	5.9% (1)	8.3% (1)	3.6% (1)	0	3%
12 months	5.7% (2)	0	0	3.6% (1)	0	3%
18 months	2.8% (1)	0	0	3.6% (1)	12.5% (1)	3%
I don´t remember	45.6% (16) *	47.2% (8)*	24.9% (3)	10.7% (3)	12.5% (1)	31%
Total	**35**	**17**	**12**	**28**	**8**	**100**

*The marked groups were statistically significant ($p < 0.05$) in comparison to the other groups in the same row

to do it. Surprisingly, only 13 cases (50% of the urodynamic investigated patients) actually revealed SUI – Table-3.

Although urodynamic results were recommended, only 28.5% (4/14) of the anterior colporrhaphy proceeded to it, while 44.4% (4/9) of the bladder suspension cases (Burch + abdominal bladder suspensions) and 66.6% (18/27) of the sling patients (TVT + TOT) had the exam despite doctor´s recommendations. Interestingly, only 33.3% (18/6)

Table 3 – Results of the urodynamic evaluation requested after ascertainment of clinical failure of the SUI operation.

	Anterior colporraphy	Burch	Abdominal suspension	TVT	TOT	Total
N	35	17	12	28	8	100
Urodynamic requested	14	4	5	21*	6	50
Urodynamic done	4	2	2	13*	5	26
Urodynamic SUI confirmation	4	2	1	3	3	13
ISD	4	2	1	1	1	9
Urodynamic Detrusor overactivity	1	1	1	4	3	10
Poor compliance	0	0	1	2	1	4
Obstruction (Pdet > 30 cmH_2O)	0	0	1	2	1	4
ISD + detrusor overactivity	1	1	0	1	1	4

*The marked groups were statistically significant ($p < 0.05$) in comparison to the other groups in the same row

of the cases treated with sling techniques had leakage confirmed on urodynamic evaluation, whereas the others (72.8%) had diverse urodynamic findings for their failures.

Among the cases of anterior colporrhaphy, bladder suspensions or slings, 20%, 41.4% and 19.4%, respectively, could not remember the type of the exam they were recommended, whereas 34.3%, 13.7% and 8.3% of the patients were not offered any type of further examination to diagnose the failure.

Taken together, patients submitted to anterior colporrhaphy and abdominal bladder suspension techniques were recommended more often to have static exams than those with more contemporary sling techniques, whereas functional exams centered on urodynamic investigations were the mainstay to clarify the clinical failures.

As the treatment failure became evident for the patient, alternatives to overcome the failure by the primary surgeon were explored. For the failed anterior colporrhaphy, pelvic exercises were offered to 40% (14/35) of the cases, while 14.2% received anticholinergics and 14.2% were suggested to receive further slings. No bulking agents or Botox injections were offered to this group. The patients with failed abdominal techniques were recommended to try pelvic exercises in 31% (9/29) of cases, anticholinergics in 31% and sling operation in 27.5%. Those who had received slings (TVT+TOT) were offered pelvic exercises in 13.8% (5/36) of cases, anticholinergics in 52.7% (19/36) and repeated slings in 5.5% (2/36). This group also had Botox injection offered in 8.3% (3/36) of cases and tape pull-down in 5.5% (2/36).

Anticholinergic trials to control the remaining urinary leakage (if de novo or associated with previous overactive bladder) were more common in the contemporary series involving sling techniques, with 52.8% (19/36) of patients offered this option.

As patients realized failures, they left the doctors for diverse reasons. In the words of the patients, Table-4 lists the doctor´s response to their demands for further improvement or justification for the clinical failure. As seen from the patients´ perspectives, many doctors could not justify the failure or gave evasive answers to the

Table 4 – Reasons why you stopped inquiring solution to the doctor that primarily treated you.

Reasons to stop demanding treatment by the primary doctor	Anterior colporraphy	TVT	Burch	Abdominal bladder suspensions	TOT
Doctor said sometimes it happens	3	4	2	2	1
My anatomy was awkward	2	2	1	1	0
It will solve soon	9*	6	5	2	2
The other alternatives was too demanding	0	4	1	0	2
Doctor said it was my impression/could be psychological	7	1	2	0	0
I did not want to pass over another operation as the unique alternative	1	6	2	2	1
It might take longer for the final result	9*	1	1	1	1
I decided not to mention the problem any more	1	0	0	1	0
I just quit complaining	0	2	0	0	0
I resigned	1	0	2	3	0
I naturally improved	2	2	1	0	1
Total	**35**	**28**	**17**	**12**	**8**

*The marked groups were statistically significant ($p < 0.05$) in comparison to the other groups in the same row

problem, leading the patient to leave that particular attending doctor. Thus, evasive and vacuous answers such as “It will resolve soon”, “It might take longer for the final result” or “The doctor said sometime this happens” led patients to abandon their respective doctors in 60% of the anterior colporrhaphy group, 39% of the TVT group, 46% of the Burch group, 41.6% of the abdominal bladder suspension group and 50% of the TOT group.

Because the reasons to accept treatment failure or continue with the same doctor might differ from those associated with switching doctors, a further exploration of that issue was also performed.

As shown in Table-5, when the doctor positioned himself as unable to do any further treatment of the failed case, that attitude surfaced as the main reason for the patient to leave that particular doctor.

When the patients were asked if they warned their primary doctor about changing doctors, 98% said they did not mention it. However, they recalled that 43% of their primary doctors recommended them to seek an expert because the problem could not be solved by the primary doctor.

DISCUSSION

Surgical treatment failure for SUI is a recognized and current phenomenon (2, 8) contributing to resentment of the doctor and loss of confidence leading to poor adherence to follow-up regimens. Many studies focus on the long-term results, but our data reveal that unsatisfactory results may be evident with only 6 months of follow-up (60%).

The nature of patient loss to clinical follow-up is vague, being poorly studied or understood (6, 9, 10). Although little attention is paid to the loss of patients to follow-up, if such patients account for more than 10% of a given protocol, the validity of the results may not be consistent and reproducible, as already stated (11, 12).

Oncological protocols and treatments may be easier to gauge, as primary or secondary end-

Table 5 – Reasons why you change doctor.

Reasons to change doctor	Anterior colporraphy	TVT	Burch	Abdominal bladder suspensions	TOT
I lost confidence on the doctor	4	3	4	4	2
He said he couldn´t do any further	1	2	2	1	0
He said "It will solve soon" but it didn´t	11*	9*	6	4	3
The alternatives were demanding/painful	2	2	2	0	0
He said my case was "final"	2	5	2	2	1
He could not explain why that happened	2	1	1	1	0
He changed medications with no clinical result	3	1	0	0	1
My family/friend said I should seek another opinion	2	0	0	0	0
He deviated from the central problem	4	2	0	0	0
Changed health insurance - the doctor was not aligned to it	2	2	0	0	1
Changed city	2	1	0	0	0
Total	**35**	**25**	**17**	**12**	**8**

*The marked groups were statistically significant ($p < 0.05$) in comparison to the other groups in the same row

-points are objectively measured, while functional diseases are submitted to subjective, cultural and emotional backgrounds. The reasons patients do not proceed to further therapy to reach what is considered a satisfactory clinical result are not clearly understood. Such reasons may depend on the doctor´s capacity of persuasion, optimism and reliance, all of which are founded on cultural and personal factors. As patients recognize the failure, the manner in which the doctor explains the failure seems to negatively affect the patients´ perception, leading them to abandon that particular doctor. The reasons patients change doctors are not always related to the reasons they disbelieve in the treatment or failures. As our data show, refraining from complaining about urine leakage is not associated with leaving the doctor, which seems to be more associated with doubt and a lack of reasonable explanations for the unsuccessful operation.

Patients change doctors without informing the doctors or obtaining their consent more often than we think. This behavior negatively affects the doctor´s self-perception of failure and success, deluding them about proper surgical techniques and personal cumulative results. This discrepant view of lost follow-ups may involve inter-personal or cultural aspects, as 98% of our studied patients did not notify the primary doctor about changing professional care, with many offering a lack of trust in the doctor to justify the change. This finding provides new insight into the patient-doctor relationship, highlighting the false perception of success by doctors if the patient does not show up for follow-up, especially in private care systems.

Our study was very restricted in enrollment, using only patients treated for SUI which demanded long-time to enroll 100 cases. We kept all the filled-out questionnaires throughout the years, as this project required long-term data gathering before solid conclusions could be made for this particular subset of surgically treated cases.

The reasons why patients do not attend sequential follow-ups as pre-operatively recommended is not clear, but Ballert et al. stated that the most common reason for not returning was that the patient was satisfied and believed that returning was not necessary despite the pre-operative recommendation. There is no discrepancy in clinical results between those attending personally or only answering telephone queries on academic studies, as the authors reported that the success rates in these two types of follow-up were the same at 3 months, but they did not state any rates beyond that time. Interestingly, 20% of their cases that could not be accessed by validated tools at 3 months of follow-up had undergone a secondary intervention; this observation revealed a clustering of cases that were not evaluated in the early follow-up because of severe urinary problems. Similarly, the same author also discovered that patients dismissing follow-up did not return because of clinical failure and dissatisfaction (9). In a previous article from Ou et al., 58% of the 71 identified articles did not comment on the lost-to--follow-up patients (10). Although these authors identified approximately 10% as not returning due to work, death or other reasons, our population clearly indicated disappointment and a lack of confidence as the main reasons to quit on treatment and follow-up.

Cured patients believe that reevaluation is not necessary, while those who were unsuccessfully treated seek another doctor´s opinion or stop receiving treatment. We cannot comment on that issue, as our population is exclusively composed of failed cases looking for cures from a secondary surgeon.

We do not know how frequently this phenomenon occurs in community health-care centers or private health-care systems where many doctors options are available, but reports varied from 0 (6) to 100% (7) even in academic studies (1,7). This poorly studied issue seems to concentrate on a biphasic response with peaks in the first 3 months to 1 year and later than 3 years after the surgical treatment. In the first phase, those not returning may not come to the office, but they still comply with some academic requirements, such as answering questionnaires after contact by letter or telephone, while others may disappear because they might have moved or died, be dependent or frail, or simply do not want to comply any further (6,7).

Some authors assert that the failure of continuous clinical follow-ups is due to permanent clinical success, whereas others claim that the lost follow-ups are related to clinical failure

leading to patients' doubt and loss of confidence in additional therapeutic procedures. Assuming patients lost during follow-up as successes or as failures can markedly shift the rate of failure or success in a given technique or series, as prospectively demonstrated by Ward et al. (13) and Minassian et al. (14). Assuming them as failures or cured does not mean that long-term follow-up will be persistent and consistent because objective and subjective results regularly do not match perfectly (2), and recurrence and failure may become obvious only after a long-term follow-up (7,15), rendering conclusions on the long-term efficacy of the procedure more difficult to state.

An additional factor of decreased adherence to follow-up is related to the complexity of clinical follow-up schedules in academic or prospective protocols as noted by Singh M et al., who observed 9.3% refusals and 16.6% loss to follow--up despite 3 telephone contacts in 108 operated cases. Surprisingly, even after consenting to the protocol and the office evaluations, only 52% of all of the consenting cases completed their voiding diaries, questionnaires and pad-tests as ordered (16). The invasive nature of some exams, such as urodynamic investigations in our population, might explain the reasons that patients refused to continue further investigation after clinical evidence of failure. Here, the half-half law applied to this population, as half of patients were recommended to have urodynamic investigation and only half of them complied (~25%), although they underwent urodynamic studies later by the hand of a second surgeon at our referral center.

While our population was composed exclusively of failed cases, the scenario of patients changing doctors without completing the exams requested by the primary doctor is very common in clinical practice, and it may reflect the lack of trust on the first surgeon to fix the problem.

Although we could not consistently critique the nature of the proposed investigative exams, it surprised us that urodynamic studies and cystoscopy were so infrequently recommended to rule out any other cause related to failure. Post--operative urodynamic investigation was rarely requested for the abdominal bladder suspension or anterior colporrhaphy groups, most likely reflecting an older view of causes for failure compared to the more contemporary suburethral sling cases in which functional exams seem to more accurately reflect the causes of the failures than static imaging evaluations.

In this regard, urodynamic study done after ascertainment of failure confirmed pure SUI as the main cause of leakage in only 50% of the cases with another half revealing other urodynamic reasons for the clinical failure.

While, as a rule, a lack of aggressive investigation for failures was observed it was evident that second treatment must be refrained without appropriate investigation.

It is amazing to realize that doctors do not investigate failures aggressively as they should, justifying themselves by asserting the symptoms will resolve by themselves soon, in contrast to clinical attitudes regarding oncological recurrences. Likewise, numerous case-load studies access patients on regular follow-up, while the recurrent cases or those simply electing to tolerate leakage are poorly studied or dismissed from the results.

It can be seen that failures from slings led doctors to offer medications more frequently than failures from abdominal route techniques, where changing to slings operations stood as the ultimate option for treatment failure. In this regard, only a few doctors proposed a second sling as an alternative to correct the failed one. Doctor's embarrassment in trying to explain the failure possibly accounts for a more aggressive investigation attitude.

Contrary to the findings by Minassian et al. (14), who stated that only 1.85% of patients' dissatisfaction with the surgery as the main reason for poor compliance of follow-up, we noted a poor relationship with doctors and doubt for further treatment as the main reason for poor adherence. In their study, 26.8% (29/108) had poor follow-up although the clinical result could be checked by telephone interview in 15.7% (17/108) of those not returning or put in another way, 11.1% (12/108) were true missing cases despite the prospective nature of the study. Being one of the few reports on this issue, the mentioned authors concluded that the patients with good follow-ups present a higher success rate (92.4%) than those with poor reevaluation (72.4%), who additionally

showed abandonment of follow-up earlier (mean 21 versus 10 months) (14).

Academic protocols with randomized and non-randomized prospective studies were investigated by Ou et al., who revealed an incidence of patients lost to follow-up of 8.1% at 12 months, 28% at 24 months and 36% at 36 months (10). In contrast to their results, our recent study (7) revealed a much earlier patient loss to follow-up, with 10.2% of the patients not returning personally for examination at 6 months and 25% not returning at 12 months, whereas others described lack of physical examination in 100% at 5 years of follow-up (7). These observations occurred even though patients were operated on by the same surgeon at the same center, acknowledging that more stringent efforts to contact the patients must be pursued to create more solid doctor-patient relationships. These results highlight the need to constantly check on clinical results to ensure improvement.

Missing patients must be more deeply studied because we do not know the reasons they simply disappear from consecutive evaluations after an operation that is somehow meaningful to any lay person. We can speculate that SUI operations may represent a simpler operation on the lay´s conception due to the lack of prolonged hospitalization, immediate return to feeding and minimal discomfort despising the necessity for follow-up.

This population demands attention because unraveling the failures or demanding investigation does not happen on oncological counterpart treatments, be it clinical or surgical, with reevaluation accurately followed and more actively investigated and pursued by doctors and patients.

We concluded that doctors may overestimate their success rates due to the lack of prolonged and consistent follow-up for functional or anatomical diseases, as surveys display better ways to check results than charts (4).

However, this paper has flaws: 1- although prospective in nature, the majority of the information was collected from patients´ experiences, treatment references or from the past attendant doctor suggesting recall bias; 2- many missing parameters may be biased by emotional resentment; 3- not allowing direct and precise access to file reports may promote incorrect information; 4- even when urodynamic/cystoscopy was performed on a single patient, it cannot be certain that the test was related to investigative purposes of clarifying SUI failure or any other reason; 5- only those who failed and who recently sought medical treatment/evaluation were studied.

Although these flaws may be disturbing and confounding, the core conclusions center on the fact that patients abandon their doctors after a failed case for different reasons, although the doctor´s attitude regarding intangible parameters such as confidence and active investigations to clarify the causes of the failure play important roles in this relationship.

CONFLICT OF INTEREST

None declared.

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Appendix

Questionnaire used to evaluate treatment failures for SUI

1 - How long did you take to realize the operation did not work?"

1 month	( )
3 months	( )
6 months	( )
9 months	( )
12 months	( )
18 months	( )
I don´t remember	( )

2 - "What was offered to investigate or diagnose the causes of the failure"

Cystosocpy	( )
IVP	( )
Cystography	( )
CT	( )
MRI	( )
Laparoscopy	( )
Urodynamic investigation	( )
No investigation was offered	( )
I don´t remember/ I don´t know the exam	( )

3 - "What was offered to treat the undesired results from the SUI operation?"

Pelvic exercises/physiotherapy	( )
Pesaries	( )
Anticholinergics and/or pelvic exercises	( )
SUI correction through abdominal route	( )
Primary slings	( )
Repeat sling	( )
Attempt to pull-down or release the tape	( )
Bulking injections	( )
Botox injection	( )
Unknown/Not remembered	( )

4 - "Reasons why you stopped demanding solution by the doctor that primarily treated you"

Doctor said sometimes it happens	( )
My anatomy was awkward	( )
It will solve soon	( )
The other alternatives were too demanding	( )
I did not want to pass over another operation as the unique alternative	( )
Doctor said it was my impression/could be psychological	( )
It may take longer for the final result	( )
I decided not to mention the problem any more	( )
I just quit complaining	( )
I resigned	( )
I naturally improved	( )

5 - "Reasons why you change doctor"

I lost confidence on the doctor	( )
He said he couldn´t do any further	( )
He said "It will solve soon" but it didn´t	( )
The alternatives were demanding/painful	( )
He said my case was "final"	( )
He could not explain why that happened	( )
He changed medications with no clinical result	( )
My family/friend said I should seek another opinion	( )
He deviated from the central problem	( )
Changed health insurance - the doctor was not aligned to it	( )
Changed city	( )

6 - "Did you warned/said your doctor you would seek another opinion?

Yes ( ) No ( )

7 - Were you recommended by your doctor to seek another opinion?"

Yes ( ) No ( )

ORIGINAL ARTICLE

Vol. 40 (6): 802-809, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.11

Patients lost to follow-up after midurethral sling surgery: How are they?

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ABSTRACT

Purpose: To assess the ratio of patients lost to follow-up (FU) after midurethral sling surgery, to evaluate their success rate and current status, and to identify the reasons for FU loss.

Materials and Methods: Two-hundred thirty-eight patients who received trans-obturator tape (TOT) surgery were reviewed. For patients lost to FU within 3 months, Stamey's outcome questionnaire and questions regarding the reasons for FU loss were submitted via phone interview.

Results: One hundred forty-three (60.1%) patients (FU loss group) were lost to FU within 3 months postoperatively. In the FU loss group, phone interviews were conducted with 117 (81.8%) patients. Aside from the urgency rate (59.3% vs. 72.3%, p=0.049), there were no significant statistical differences in preoperative profiles between two group. The success rate of the FU loss group (80.3%, 94 of 117 patients) was lower than that of the FU group (95.8%, 91 of 95 patients) (p=0.001). The success rates in the FU loss group with mixed urinary incontinence (MUI) were significantly lower than in the FU group with MUI. As for the reason for FU loss, 74 patients (62.7%) were lost due to incontinence improvement, 19 patients (16.1%) cited personal problems, and 5 patients forgot the next follow-up date. Only 10 patients gave up further treatment despite their persisting incontinence.

Conclusions: In our study, more than half of patients were lost to follow-up after midurethral sling surgery. The FU loss group showed a lower surgical success rate, particularly with MUI. Close FU is recommended for better consultation of patients' incontinence.

ARTICLE INFO

Key words:
Urinary Incontinence; Suburethral Slings; Treatment Outcome; Questionnaires

Int Braz J Urol. 2014; 40: 802-9

Submitted for publication:
April 03, 2014

Accepted after revision:
October 19, 2014

INTRODUCTION

Stress urinary incontinence (SUI) is a widespread problem estimated to affect over 26% of middle-aged women in America and it induces social, sanitary, and psychological problems related to the patients' quality of life (1). Recently, considerable progress has been made toward treatments of SUI stemming from advances in understanding the pathogenesis (2-5). Various new surgical treatments that are safe, convenient, and less invasive have been introduced (6-8). In particular, the mid-urethral sling surgeries (MUSSs) substitute for other previous treatments and have emerged as the new gold standard (9).

The MUSS was initially described as a Tension-free vaginal tape (TVT) procedure by Ulmsten et al. in 1995 (6). Afterwards, the Suprapubic arc (SPARC) and Trans-obturator vaginal tape (TOT) procedures were introduced to lessen the compli-

cations such as bladder or bowel injuries. In less than ten years, these MUSSs spread worldwide. Various studies have demonstrated that all types of MUSSs have equivocally high long-term treatment rates, as well as low complication rates (10-13).

In clinical practice, however, it has been our empiric observation that a considerable fraction of SUI patients are lost to follow-up after MUSSs. Most previous reports have disregarded the results of those lost to regular follow-up (14-17), and there is relatively little information in the literature regarding missing patients after MUSSs. We hypothesized that these follow-up loss patients may have different results after MUSSs.

To test this hypothesis, we contacted our follow-up loss patients by telephone. We investigated the reasons for follow-up loss and the treatment success rate in these patients.

MATERIALS AND METHODS

A retrospective analysis was conducted of all patients who underwent outside-in type TOT (Monarc®; AMS Inc., MN, USA) by single surgeon (Son H) between January 2003 and December 2008 for SUI. The study group included 238 women with a mean age of 55.8 (±9.7, SD) years. The protocol of the current study was approved by the Institutional Review Board of SMG-SNU Boramae Medical Center, Seoul, Korea (IRB No. 06-2009-28).

The operative technique was modified from DeLorme et al. (18, 19). The patients were put in lithotomy position. A vertical midline vaginal incision was made and the peri-urethral tissue was dissected laterally from the incision. Bilateral puncture incisions were made lateral to the ischiopubic ramus. The tunneller was introduced through the skin incision and crossed the obturator membrane. The index finger was placed into the vaginal incision to guide the tunneller. The end of the tape was introduced into the eye of the needle and then pulled through to place it behind the urethra without tension. The vaginal incision was repaired, and the Foley catheter and the vaginal gauze packing were indwelling until the first postoperative day.

Based on follow-up records, patients were divided into two groups: the follow-up loss group (FU loss group) with loss within 3 months after the surgery and the follow-up group (FU group) with current follow-up. The following preoperative parameters were collected from the clinical records: age, body mass index (BMI), comorbidity, previous gynecologic surgery, symptom duration, symptom severity, International Prostate Symptom Score (IPSS), voiding diary, urinalysis, uroflowmetry (UFM) with post-void residual volume (PVR), 1hr pad test and Q-tip, and urodynamic study findings, including valsalva leak point pressure (VLPP) and cough leak point pressure (CLPP).

The routine interval for follow-up was 1, 3, 6 and 12 months after the surgery. Careful interviews, UFM and PVR measurement were performed in the FU group. Additional telephone interviews were conducted for the FU loss group. The questionnaires used in the phone interview were written at our institute (Table-1). Questionnaires were designed in previous studies to determine the following: the current states of SUI, the reason for follow-up loss, subjective satisfaction, and complications after the surgery in the FU loss group (20-24).

Surgical outcomes were grouped into 3 categories according to the continence grading described by Stamey (25). These were as follow: cure, defined as a no leakage of urine; improvement, defined as minimal leakage without subjective discomfort; and failure, defined as no change in incontinence or with subjective discomfort. Treatment success was defined as the cure or improvement of presenting symptoms by the time of this survey.

The patients' baseline characteristics, preoperative data, and surgery outcomes were compared between the two groups. We also analyzed the reasons for the follow-up loss in the FU loss group by referring to the results of questionnaire. Comparisons between the two groups were made with the Student's t-test or paired t-test for continuous variables, chi-square or Mann-Whitney U test for nominal variables using SPSS® (version 21.0; IBM, NY, USA). All p-values were two-sided with significance considered at $p < 0.05$.

RESULTS

Of the 238 treated patients, 143 (60.1%) were allocated to the FU loss group and 95 (39.9%)

Table 1 - Telephone interview questionnaire for follow-up loss group.

1. Why didn't you return to the hospital after the surgery?
A. Symptom improvement.
B. Private problems
C. Abandonment of additional treatments
D. Others
2. What is your current SUI status after the surgery?
A. No leakage
B. Minimal leakage, without subjective discomfort.
C. Leakage is decreased, but discomfort.
D. No change after the surgery.
E. Deterioration after the surgery
3. Do you think the SUI surgery improved your incontinence symptoms?
A. Yes
B. No
4. Are you satisfied with the outcomes after the surgery?
A. Yes.
B. No.
5. Did you have any other complications after the surgery?

to the FU group. Mean time from surgery was 19.6 (±9.9) months for FU loss group vs. 26.7 6 (±12.7) for FU group. There were no significant differences between the two groups in baseline characteristics and preoperative findings except in the comorbid urgency rate. The compared parameters included age, BMI, symptom duration, symptom severity, comorbid urgency or urge incontinence, previous surgery, IPSS, preoperative UFM with PVR, 1hr pad test, and urodynamic study findings. Detailed data for the two groups are shown in Table-2.

120 (83.9%) of the 143 FU loss patients were contacted for the telephone interview. Two patients refused to respond, and one patient had died before the interview for reasons unrelated to the TOT procedure. Consequently, 117 patients (81.8%) in the FU loss group were interviewed. The overall treatment success rate in the FU group was 95.8% [91 of 95 patients, "cure" in 78 (82.1%) and "improvement" in 13 (13.7%)]. FU group showed significant improvement of IPSS-total (sum of question 1 to 7; 20.5 vs. 6.9, $p < 0.001$), IPSS-voiding (sum of question 1, 3, 5, and 6; 10.0 vs. 2.5, $p < 0.012$) , IPSS-storage (sum of question 2, 4, and 7; 10.5 vs. 2.5, $p < 0.001$), and IPSS-QoL (quality of life question score; 4.8 vs. 1.5, $p < 0.001$), respectively (table was not given). According to the interview responses from the FU loss group, the success rate was 80.3% [94 of 117 patients, cure in 82 (70.1%) and improvement in 12 (10.2%)]. There was a statistical difference in treatment success rates between the two groups ($p = 0.001$) (Table-3).

The status of SUI could be determined in 212 patients (95 in the FU group, and 117 in the FU loss group). In 204 of the 212 patients, the presence of preoperative urgency and urge incontinence was identified through review of medical records. The 204 identified patients were classified into two subgroups: stress type incontinence and mixed type incontinence. In each subgroup, the treatment success rates for the FU group and the FU loss group were compared. Among the 131 patients in the mixed type incontinence subgroup, there was a significant difference in success rate (95.5% in FU group vs. 76.6% in FU loss group, $p=0.002$). However, among the 73 patients in the stress type incontinence subgroup, there was no statistically significant difference (96.3% in FU group vs. 82.6% in FU loss group, $p=0.086$) (Table-4).

In the FU loss group, the reasons for follow up loss were identified for 118 patients (117 responders plus one deceased person) (Table-5). Seventy-four patients (62.7%) did not follow up

Table 2 - Baseline characteristics and preoperative findings.

	FU loss group	FU group	P*
No. of patients	143	95	-
Mean age (±SD, years)	55.8 (±9.6)	55.9 (±9.8)	0.929
BMI (±SD, kg/m^2)	25.3 (±3.4)	25.2 (±3.1)	0.800
DM, HTN (%)	44 (30.8%)	37 (38.9%)	0.192
Gynecologic operation (%)	18 (12.6%)	12 (12.6%)	0.992
Symptom duration (±SD, months)	56.3 (±56.4)	65.9 (±63.8)	0.250
Median Stamey grade (range)	2 (1-3)	2(1-3)	0.987
Urgency (%)	80 of 135 (59.3%)	68 of 94 (72.3%)	0.042
Urge incontinence (%)	65 of 135 (48.1%)	57 of 94 (60.6%)	0.062
IPSS-total (±SD)	15.5 (±9.3)	17.8 (±8.1)	0.464
IPSS-voiding (±SD)	7.9 (±6.5)	9.1 (±5.4)	0.193
IPSS-storage (±SD)	7.5 (±4.0)	8.7 (±3.8)	0.115
IPSS-QoL (±SD)	4.0 (±1.6)	4.2 (±1.3)	0.367
MUCP (±SD, cm H_20)	56.5 (±22.9)	52.8 (±21.4)	0.213
MCC (±SD, mL)	407.0(±85.3)	384.6 (±100.6)	0.133
VLPP (±SD, cm H_20)	85.9 (±32.7)	85.1 (±27.6)	0.838
CLPP (±SD, cm H_20)	101.5 (±36.5)	104.1 (±34.0)	0.590
Q-max (±SD, mL/sec)	33.5 (±29.2)	31.7 (±19.9)	0.577
Q-tip >30° (%)	59 of 140 (42.1%)	30 of 94 (31.9%)	0.131
1hr Pad test (±SD, gm)	48.8 (±58.5)	39.3 (±37.7)	0.152
Voided volume (±SD, mL)	228.8 (±102.7)	243.2 (±98.4)	0.278
PVR volume (±SD, mL)	21.4 (±63.2)	23.0 (±37.3)	0.825
FBC (±SD, mL)	379.9 (±131.7)	380.6 (±136.6)	0.972

FU loss group = follow-up loss group; **FU group =** follow-up group; **BMI =** Body mass index; **IPSS =** International Prostate Symptom Score; **IPSS-total =** sum of question 1 to 7; **IPSS-voiding =** sum of question 1, 3, 5, and 6; **IPSS-storage =** sum of question 2, 4, and 7; **IPSS-QoL =** quality of life question score; **MCC =** maximal cystometric capacity; **VLPP =** valsalva leakage point pressure; **CLPP =** cough leakage point pressure; **Q-max =** peak flow rate on uroflowmetry; **PVR =** volume, post-void residual urine volume; **FBC =** functional bladder capacity; * = by Student's t-test (continuous variable), chi-square test (binary categorical variable), and Mann-Whitney U test (categorical variable more than three)

Table 3 - Outcome of the surgical procedure in two groups.

Outcome	FU loss group	FU group
Cure	82 (70.1%)	78 (82.1%)
Improvement	12 (10.2%)	13 (13.7%)
Failure	23 (19.7%)	4 (4.2%)
Total	117 (100%)	95 (100%)

FU loss group = follow-up loss group; **FU group =** follow-up group

Table 4 - Treatment success rate for the two groups stratified by accompaning symptoms.

	FU loss group	FU group	P
Mixed type incontinence	76.6% (n=64)	95.5% (n=67)	0.002
Stress type incontinence	82.6% (n=46)	96.3% (n=27)	0.086

FU loss group = follow-up loss group; **FU group =** follow-up group

Table 5 - Reasons for follow-up loss after the mid-urethral sling surgery.

Reason	N	Percent
Symptom improvement	74	62.7%
Personal problem	19	16.1%
Abandonment of additional treatment	10	8.5%
Oblivion of the follow-up date	5	4.2%
Death	1	0.8%
Other reasons	9	7.6%
Total	118	100

because of symptom improvement. Other patients were lost due to private matters, including 19 (16.1%) patients with financial or private problems and 10 patients (4.2%) who abandoned additional treatment despite their ongoing incontinence. Five patients (4.2%) forgot the follow-up dates. Among the 117 responders in the FU loss group, 98 patients (83.8%) thought that TOT improved their symptoms, and 85 patients (72.6%) were satisfied with the outcome of the surgery. Two patients (1.7%) experienced de novo urgencies after surgery.

DISCUSSION

This study showed that 60.1% of patients with TOT for SUI were lost to follow-up within 3 months. There are not many reports about follow--up loss after MUSSs, but a few studies reported 27 to 31% loss rate within 3 months (26, 27). Ou et al. [28] performed systematic review of 58 prospective SUI surgery series and reported 36% follow--up loss at 36 months after surgery. Our loss rates were higher than those of previous reports. The cultural differences, the educational and financial statuses of local populations, the differences in the medical systems, and the intensity of follow-up recommendation between clinical studies and real practices could be reasons for the differences in follow-up rates. In real-life practice, stress urinary incontinence is not a life-threatening disease; thus the discrepancy of follow-up compliance may be exaggerated.

Many factors may have influenced the patients who did not follow-up. Symptom improvement after surgery is postulated as the major cause. Indeed, our findings show that 62.7% patients are lost to follow-up because of symptom improvement (Table-5). These results are in close agreement with Ballert et al. (26), suggesting that a substantial portion of patients lost to follow--up were satisfied with treatment and discontinued the planned follow-up by their own decision. In the current study, personal problems such as busyness or financing problems were the second largest (16.7%) causes. However, a considerable fraction of these patients may have experienced symptom improvement. Such improvement might

have promoted the follow-up loss because of their private problems. Even though the number of such cases was low, some patients (4.2%) were lost to follow-up because they had forgotten their next appointment dates. In practice, patients could be reminded of the next follow-up appointment. However, a considerable portion of patients abandoned their further treatment despite their remaining symptoms. Some may have visited other hospitals.

Evidence continues to accumulate indicating that the overall outcomes of MUSSs are excellent. In outside-in type TOT, well-designed prospective studies have shown that the treatment success rate is 86% to 94% in up to 4-year follow--up (14-16). However, all these studies reported some fraction of follow-up loss (4% to 14%) and missing data were excluded from the analyses (complete case analysis). However, processing the missing data is a complicated issue. Karl et al.(29) recommended considering the full range of best (all cases are successes) and worst (all cases are failures) scenarios in handling loss of follow-up data. In this manner, Ward et al.(30, 31) reported an extremely broad range of success rates after TVT: 63% to 85% in 2 years and 33% to 82% in 5 years. Ou et al. (28) pointed out that only 7 of 58 SUI prospective studies considered the missing data as failure. This exclusivity of complete case analysis may exaggerate the outcomes of MUSSs.

In our analysis, the overall treatment success rate was 95.8% in the FU group (Table-2). This result is consistent with previous TOT series. However, we found a significant difference in the treatment success rates between the FU group and FU loss group, (95.8% vs. 80.3, p=0.001). In a previous study, Ballert et al. (26) concluded that there are no significant differences in success rates (follow-up loss vs. follow-up: 73% vs. 81%, p=0.39). However, they were only able to contact about two-thirds of follow-up loss patients. We had a higher response rate of follow-up loss patients (81.8%). The results of the present study correspond with the results from Minassian et al.(27), which reported that follow-up loss patients had lower success rates (72.4% vs. 92.4%, p=0.006).

SUI subtypes were not considered in previous studies (26, 27). To clarify this point, the patients were classified in two subgroups: mixed type incontinence and stress type incontinence. In mixed type incontinence, there was a statistically significant difference in success rates between the two groups (95.5 % vs. 76.6%, p=0.002). In stress type incontinence, however, there was no significant difference (p=0.086). These results are in agreement with those of a previous study reporting that more than half of treatment failure patients in the follow-up loss group had a higher urge score ratio than stress score ratio based on the Medical, Epidemiological and Social Aspects of Aging (MESA) questionnaire [26]. We postulated that, in the FU group, the remnant urgency or urge incontinence after MUSS may be settled by additional treatment; on the other hand, in the FU loss group, these supplementary aids were not utilized. With these findings, we suggest that the mixed type incontinence patients need to be followed more closely than simple stress type incontinence patients.

In our experience with the telephone interview with follow-up loss patients, in the event of successful contact, nearly all patients responded well to the survey (98.3% 117 of 119). The merit of the telephone interview is that the current states of follow-up loss patients were determined with ease. We simplified the questionnaires to optimize the response. However, our study design has an important limitation in that the results are dependent on the patients' replies, without any objective findings. Another limitation of the current study is the relatively high rate of follow-up loss. Possible reasons for this higher incidence were mentioned above. The retrospective study is also a pitfall. However, by simplifying the study design, we could identify the current status of most patients who were lost to follow-up after MUSS and thus fulfill our initial purpose. Patients lost to follow-up after MUSSs are often excluded because of the difficulty in identifying their current status. As a result, there is relatively little information in the literature regarding these follow-up loss patients. Our current study reconsidered these neglected patients. Further long-term and intensive studies are required to assess these follow-up loss patients. Furthermore, the status of FU loss patients must be considered in order to study the long-term outcomes of the MUSSs.

CONCLUSIONS

The current study demonstrated that a considerable fraction of patients were lost to follow up 3 months after MUSSs. Moreover, there was a significant difference in treatment success rate, especially between the FU and FU loss groups in the mixed type incontinence subgroup. Based on these findings, we recommend that mixed type incontinence patients should be followed up more closely.

ABBREVIATIONS

SUI = stress urinary incontinence
MUSS = mid-urethral sling surgery
SPARC = suprapubic arc
TOT = trans-obturator vaginal tape
FU = follow-up
BMI = body mass index
UFM = uroflowmetry
PVR = post-void residual volume
VLPP = Valsalva leak point pressure
CLPP = cough leak point pressure
MESA = Medical, Epidemiological and Social Aspects of Aging

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 810-815, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.12

Robotic repair of vesicovaginal fistulae with the transperitoneal–transvaginal approach: A case series

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ABSTRACT

Objective: To describe a novel technique of repairing the VVF using the transperitoneal-transvaginal approach.
Materials and Methods: From June 2011 to October 2013, four patients with symptoms of urine leakage in the vagina underwent robotic repair of VVF with the transperitoneal-transvaginal approach. Cystoscopy revealed the fistula opening on the bladder. A ureteral stent was placed through the fistulous tract. After trocar placement, the omental flap was prepared and mobilized robotically. The vagina was identified and incised. The fistulous tract was excised. Cystorrhaphy was performed in two layers in an interrupted fashion. The vaginal opening was closed with running stitches. The omentum was interposed and anchored between the bladder and vagina. Finally, the ureteral catheters were removed in case they have been placed, and an 18 Fr urethral catheter was removed on the 14th postoperative day.
Results: The mean age was 46 years (range: 41 to 52 years). The mean fistula diameter was 1.5 cm (range 0.3 to 2 cm). The mean operative time was 117.5 min (range: 100 to 150 min). The estimated blood loss was 100 mL (range: 50 to 150 mL). The mean hospital stay was 1.75 days (range: 1 to 3 days). The mean Foley catheter duration was 15.75 days (range: 10 to 25 days). There was no evidence of recurrence in any of the cases.
Conclusions: The robot-assisted laparoscopic transperitoneal transvaginal approach for VVF is a feasible procedure when the fistula tract is identified by first intentionally opening the vagina, thereby minimizing the bladder incision and with low morbidity.

ARTICLE INFO

Key words:
vesicovaginal fistulae;
robot-assisted laparoscopic transperitoneal transvaginal approach

Int Braz J Urol. 2014; 40: 810-5

Submitted for publication:
November 18, 2013

Accepted after revision:
May 03, 2014

INTRODUCTION

Vesicovaginal fistulae (VVF) represent a significant morbidity in female urology; the incidence varies between 0.3% and 2%, most of them iatrogenic, other etiologies mentioned in the literature include pelvic trauma, radiation necrosis, illegal abortion, as well as radical pelvic surgery (1, 2). In developing countries, the main causes are obstructed labor due to poor obstetric care; meanwhile, in countries with adequate obstetric care, 90% of VVF cases are caused by gynecological procedures. Hysterectomy, both with the transabdominal and transvaginal approaches, is the most common procedure that results in fistulae, and this procedure is the cause of 75% of fistulae (2, 3).

There is currently some controversy concerning the timing of the surgery and the type of procedure that should be used to repair fistulae.

The decision between transvaginal and transabdominal approaches depends on the location of the fistula, its relationship with the ureteric orifice and the time between fistula formation and repair (3). The advantages of early vs. delayed repair are still debatable (4). The effectiveness of surgical correction of large fistulae has been described as ranging from 75% to 97%(3,5,6).

Nezhat et al. initially reported the first retrovesical laparoscopic VVF repair in 1994 (7). The largest laparoscopic series was reported by Sotelo et al. (8) using a transvesical approach that localizes the fistula tract without requiring additional vaginal incisions or further dissection of the vesicovaginal space. Once the fistula is identified, the vesicovaginal space is dissected to separate the structures; the importance of this technique lies in the intentional cystotomy for localizing the tract. The laparoscopic approach is primarily associated with similar success rates, minimal surgical trauma and reduced morbidity, allowing for more rapid convalescence (4,8, 10-16). Despite initial enthusiasm, laparoscopy has not gained popularity, most likely because laparoscopic VVF dissection and intracorporeal suturing are technically challenging. Robotic assistance in complex laparoscopic procedures has overcome the technical difficulties of the laparoscopic approach, even in challenging cases of recurrent VVF (17). Only a few reports of robotic vesicovaginal fistula repair have been described in the literature. Melamud et al. (18) in 2005 were the first to report this approach.

In this study, we present a novel technique, the robotic transperitoneal-transvaginal approach, which involves opening the vagina in order to identify the fistula tract.

MATERIAL AND METHODS

From June 2011 to October 2013, four patients underwent robotic repair of vesicovaginal fistulae with the transperitoneal-transvaginal approach.

All patients had symptoms of urine leakage from the vagina after abdominal hysterectomy. The first and fourth cases did not have any repair intention before this procedure; the second patient had a prior laparoscopic VVF repair and endoscopic fulguration failure; and the third patient had a failure of robotic VVF repair with synthetic surgical glue that was extruded through the bladder and vagina. In all cases, we identified the fistula orifice with flexible cystoscopy as supratrigonal and/or near the ureteral orifice prior to surgery, which is a reason to not favor the vaginal approach. All patients were informed about the procedure and modification of the technique, an informed consent was signed for all the patients as a rule.

Surgical technique

Robotic repair of the vesicovaginal fistulae with the transperitoneal-transvaginal approach was performed under general anesthesia by an experienced surgeon. The patient was placed in low lithotomy position, a cystoscopy was performed to confirm the fistula orifice, and a stent was inserted through the fistula tract from bladder to the vagina. Ureteral stents were placed (cases No 3 and No 4) due to the proximity of the fistula opening to the ureteral orifice. A vaginal tamponade was inserted into the vagina up to the vaginal apex, which helped in vaginal stump identification and prevention of loss of pneumoperitoneum.

Access was gained at the umbilicus with cosmetic consideration by the Hasson technique. A 12 mm port was inserted with 30° down lens, offering improved angles visulization and high definition optics that are useful when doing the anterior colpotomy; a 0° lens could be used instead. Two 8 mm robotic ports were placed symmetrically on the left and right pararectal lines. We did not use a fourth arm, with the intention of minimizing scars, but a fourth arm could be used, and an 8 mm robotic port could be placed superior to the iliac crest on the left side. A 5 mm port was placed superior to the iliac crest on the right side, between the lens and the 8 mm port, for insertion of suction irrigation assistance. The robot was docked.

All patients had adhesions; therefore adhesiolysis was performed, using a combination of sharp and blunt dissection with Maryland fenestrated bipolar forceps and monopolar curved scissors, to expose the vaginal stump and the superior aspect of the bladder. An omental flap was prepared using the open omentoplasty technique

(19), and the flap was brought down to ensure that it reaches the appropriate location between the bladder and the vagina. A stay suture was placed in the bladder using a straight needle and then exteriorized to maintain counter-traction. The needle was delivered into the abdominal cavity though the 12 mm trocar or inserted percutaneously. This counter-traction of the bladder could otherwise be performed by the robotic fourth arm. The vagina was identified with digital guidance allowing for safe insertion of the vaginal tamponade. Later the vagina was incised in a longitudinal direction according to the stent inside the fistula tract, 2 to 3 cm at level of the vaginal stump. The fistula tract was widely excised until viable fresh tissue was exposed (Figure-1). The 30° up lens allowed for comfortable tract dissection. The bladder and vagina were dissected and separated. The vaginal opening was closed with care, maintaining an overlapping suture lines using running stitches in a horizontal fashion with absorbable braided suture. Cystorrhaphy was performed in two overlapping layers in a vertical fashion with absorbable braided suture. A bladder integrity test with methylene blue was performed. Omental flap was interposed and anchored between the bladder and the vagina (Figures 2 and 3). Finally, an optional flexible cystoscopy was performed to identify the ureteral orifices; the ureteral catheters were removed and an 18 Fr urethral catheter was removed on the 14th postoperative day.

Figure 1 - Excision of the fistula tract. Notice the size of the fistula and the ureteral stent inside the bladder.

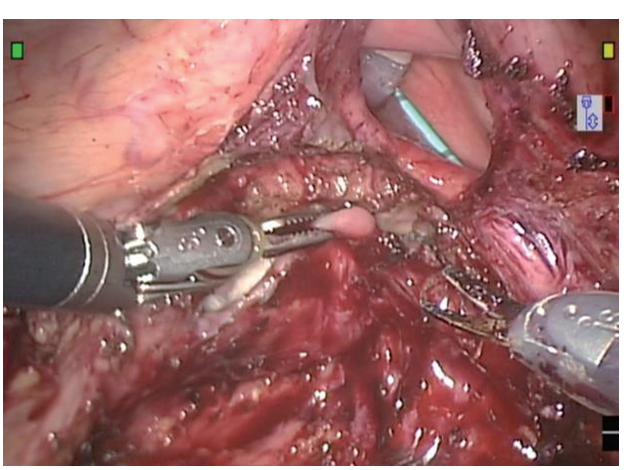


Figure 2 - Closure of the vaginal opening in a horizontal fashion with a braided suture.

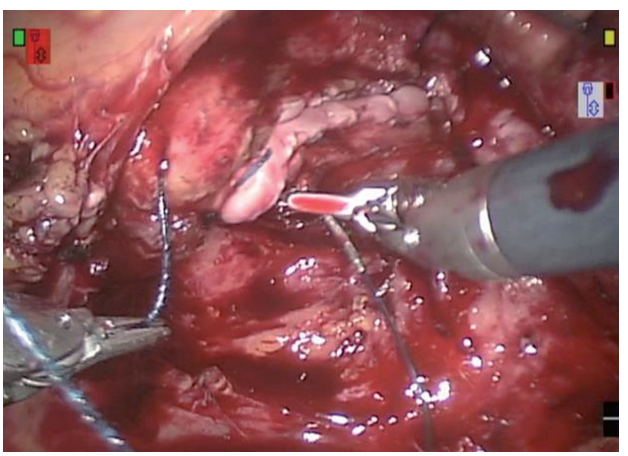
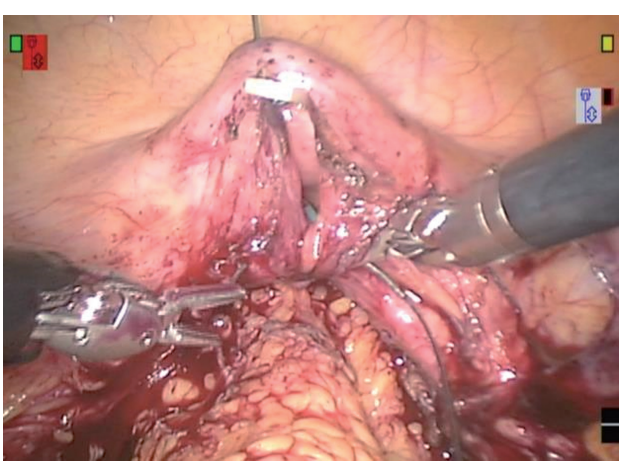


Figure 3 - Cystorrhaphy with a braided suture in a vertical fashion. Notice a suture above the bladder opening that was exteriorized to maintain counter-traction.



RESULTS

Of the 4 patients, with a mean age of 46 years (range: 41 to 52 years), 3 patients (75%) had a complex VVF. All the patients had a prior hysterectomy. The mean fistula diameter was 1.5 cm (range: 0.3 to 2 cm). The mean operation time was 117.5 min (range: 100 to 150 min). The mean console time was 77.5 min (range: 60 to 100 min). The mean estimated blood loss was 100 mL (range: 50 to 150 mL). The mean hospital stay was 1.75 days (range: 1 to 3 days). Two patients (50%) required ureteral stent placement with removal at the third

day because of the proximity between the fistula opening and the ureteral orifice. The mean drainage time was 4.25 days (range: 0 to 10 days). The mean Foley catheter duration was 15.75 days (range: 10 to 25 days). The third patient had a delay in urethral catheter removal of 25 days due to previous failure of VVF repair and patient anxiety. In all patients, the omentum was used as interposed material. With a mean follow-up time of 14.25 months (range: 1 to 21 months), none of the patients had any evidence of recurrence (Table-1).

Table 1 - Evidence of recurrence.

Age	Type of VVF	Fistula diameter (cm)	Operative time (min)	Console time (min)	Estimated blood loss (mL)	Interposed material	Hospital stay (days)	Ureteral catheterization (days)	Ureteral stent time (days)	Drainage time (days)	Urethral catheter time (days)	Follow-up time (months)	Recurrence
52	Not complex	1	120	80	150	Omentum	1	No	0	7	14	21	No
47	Complex	1.5	100	60	150	Omentum	2	No	0	0	14	17	No
41	Complex	0.3	150	100	150	Omentum	3	Yes	5	10	25	18	No
47	Complex	2	100	70	50	Omentum	1	Yes	5	0	10	1	No

DISCUSSION

Vesicovaginal fistulae are rare, but when they are present, they are devastating for women, causing distress due to persistent leakage of urine. Most vesicovaginal fistulae are the result of pelvic surgeries, wherein 90% occur after hysterectomy (1-3,4,6).

When VVFs are large or do not respond to conservative measures, surgical correction is indicated (5,6). Surgical approaches are either vaginal or abdominal (3,5). The selected approach to repair VVF depends on several factors, such as the size, number and location of fistulae, history of repair and concomitant pathological conditions. Although the morbidity of open abdominal repair is significant compared with that of the transvaginal approach, abdominal surgery is usually preferred in patients with a large (> 3 cm) or supratrigonal fistula, a fistula in close proximity to ureteric orifices and especially in patients with multiple complicated or recurrent VVFs after transvaginal repair (17). Nevertheless, the approach chosen should be that with which the surgeon is most comfortable (5,6)

Laparoscopic VVF repair by different approaches has been described. Nezhat et al. (7) were the first to report the laparoscopic retrovesical approach in 1994, which decreases the morbidity of the abdominal approach with similar success rates that range from 86% to 100% and minimal surgical trauma, allowing for more rapid convalescence (8, 10-16). Sotelo et al. (8) reported an approach in which the bladder is first intentionally opened, accurately leading to the fistulous tract without requiring additional vaginal incisions or further dissection of the vesicovaginal space. Thus, laparoscopy enables a limited cystostomy that improves upon the historically morbid O'Connor procedure, in which the bladder is bi--valved to the level of the fistula (12). Using the technological advantages of robotic technology (EndoWrist™ instruments with increased degrees of freedom leading to improved dexterity and absence of fatigue, three-dimensional [3-D] vision with improved depth perception, motion scaling, tremor filtration, higher magnification, and the surgeon's ergonomic position in a longstanding and time-consuming operation), it is possible to perform laparoscopic repair of VVF with robotic

assistance, respecting the basic surgical principles of fistula reconstruction (17).

In 2005, Melamud et al. (18) reported the first use of the robotic system for VVF repair. In the initial stages, they used standard laparoscopic instruments until the fistula was reached. Then, they completed the surgery robotically. After this initial work, additional studies performed a similar transabdominal transvesical approach with excellent results (17-25). Our results are comparable to other studies in terms of efficacy and lack of recurrence. The operation time in robot assisted laparoscopic cases ranges from 110 to 330 minutes (18, 20-24); and the mean time was 117.5 minutes. The mean estimated blood loss in our series was 100 mL, which is within the range of minimal to 150 mL reported in other studies (18, 20-24).

In this paper, we report a series of four cases undergoing a VVF repair using the robotic transabdominal-transvaginal approach, which minimizes bladder incision and may potentially reduce the recurrence rate and irritative voiding symptoms. Due to the fistulae characteristics, we preferred the transabdominal approach. When using the transvaginal approach, the vagina is first incised and the fistula tract is identified without performing a cystostomy, which is the main difference with previous robotic work (18-24). This approach is specifically useful in complex cases in patients with a history of prior surgeries whose vesicovaginal space is difficult to dissect. The limitation of our study lies in the small sample size and the lack of comparison with other techniques. We do not show evidence of a minimal incision in the vagina produce less frequent irritative symptoms than the incision in the bladder.

CONCLUSIONS

We present a novel transabdominal transvaginal robotic approach to manage VVF, which minimizes bladder incision and with low morbidity. Our approach is an attractive alternative for managing complex VVF. Robot assisted surgery offers the benefits of minimally invasive laparoscopy while providing the surgeon with enhanced vision and endowrist movements comparable to open surgery. Additional studies with a large number of patients and comparing this technique to other approaches are required to validate this novel approach.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 816-822, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.13

Relationship between kidney volume and body indexes in the Turkish population determined using ultrasonography

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ABSTRACT

Objective: To estimate the kidney volume of the healthy Turkish population using ultrasound and to evaluate the relationship between kidney volume and body indexes.
Materials and methods: Kidney ultrasound evaluation was performed on 152 patients (mean age: 42±13.7 years). Kidney length, width and thickness were measured using ultrasound. Mean total and parenchymal volume were also calculated. Patients' age, sex, weight, height and body mass index (BMI) (kg/m^2) were recorded.
Results: According to ultrasound, kidney lengths were 10.3±7.8 cm for the right and 10.4±9 cm for the left. Volumes were 158±39 cm^3 for the right and 168±40 cm^3 for the left. Volumes in women were 151.8±39 cm^3 for the right and 159.8±37 cm^3 for the left, and 164.3±38 cm^3 for the right and 175.8±41 cm^3 for the left in men. Kidney measurements correlated with body height and weight. A strong correlation with total kidney volume and kidney measurements was determined for body weight for both kidneys ($p<0.001$). A significant correlation with kidney volume and width was determined for both kidneys ($p<0.001$). A positive correlation was also found between parenchymal and total kidney volume for both kidneys ($p<0.001$).
Conclusion: The most significant factors associated with kidney volume for both kidneys in the Turkish population are kidney width and body weight. Measuring kidney volume with ultrasound is a feasible modality and is widely available for daily clinical practice.

ARTICLE INFO

Key words:
Kidney; Ultrasonography; Body Mass Index

Int Braz J Urol. 2014; 40: 816-22

Submitted for publication:
September 16, 2013

Accepted after revision:
March 19, 2014

INTRODUCTION

Ultrasonography (US) of the kidneys has replaced imaging modalities for the evaluation of kidney diseases and provides many advantages over other imaging methods (use of non-ionizing radiation, non-invasive method, little or no patient preparation, no use of medication or injection of contrast agent). It is also readily available, economical and easily reproducible to a large extent (1,2).

Kidney length and volume are important parameters in clinical settings, such as in acute and chronic renal disease and recurrent urinary tract infection (2). Previous studies have shown a direct evidence of the balance between donor graft volume and recipient metabolic demand on early graft function of transplantation patients (3). Moreover, it was reported that if the donor graft mass is inferior to recipient's BMI, the incidence of acute allograft rejection is higher (4).

In this study, we measured the kidney volumes of healthy individuals using US and evaluated the relationship between kidney volume and body indexes.

MATERIALS AND METHODS

Patients and Clinical Assessment

One hundred and fifty-two subjects (79 women, 73 men) referred to our clinic for genitourinary and abdominal US imaging were included in the study. The study population consisted of outpatients and inpatients undergoing US examination due to common clinical complaints such as weight loss, unexplained abdominal pain, nausea and constipation. We also reviewed patients' medical records and laboratory findings.

Patients' age, sex, weight, height and body mass index (BMI) (kg/m^2) were recorded. Subjects with underlying disease such as hypertension, diabetes mellitus and heart disease or any abnormal finding at US examination, such as renal cysts, hydronephrosis, single kidney, kidney stone and mass, increased parenchymal echogenicity, extreme obesity or pregnancy, or abnormal laboratory findings were excluded. The institutional ethics committee approved the study.

Sonographic evaluation

A systematic abdominal sonographic examination (4.5-5 MHz convex array transducer, Aloka alfa 6, Japan) was performed on all patients. The examination was performed with the subject in a supine and prone positions. Kidney measurements were obtained with the subject prone. Kidney length, width and thickness were measured using US. Kidney volume (total volume (Figure-1) and sinus volume (Figure-2)): lenght x thickness x width x 0.523 (5) were obtained. Parenchymal volume was calculated as total volume- sinus volume. RI was calculated automatically by Doppler US (Figure-3).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 18.0 software package (Version 18, SPSS Inc., Chicago, IL, USA). Parameters were expressed as mean±SD. Student's t-test was used to compare continuous variables. Pearson correlation coefficients were used to evaluate the strength of association between ultrasonographic parameters with each other and with other parameters, and were expressed as r^2. Statistical significance was set at $p<0.05$.

RESULTS

Three hundred and four kidneys of 152 patients ranging in age from 25 to 65 years (mean: 42±13.7 years) and undergoing US were examined. Seventy-nine patients were female and 73 male. Patients' mean age, BMI, height, weight and RI are shown in Table-1. Mean kidney lengths and total and parenchymal volumes are shown in Table-2. Mean

Figure 1 - Measurement of total kidney volume on the US image. T indicates thickness, W, width; L, length.

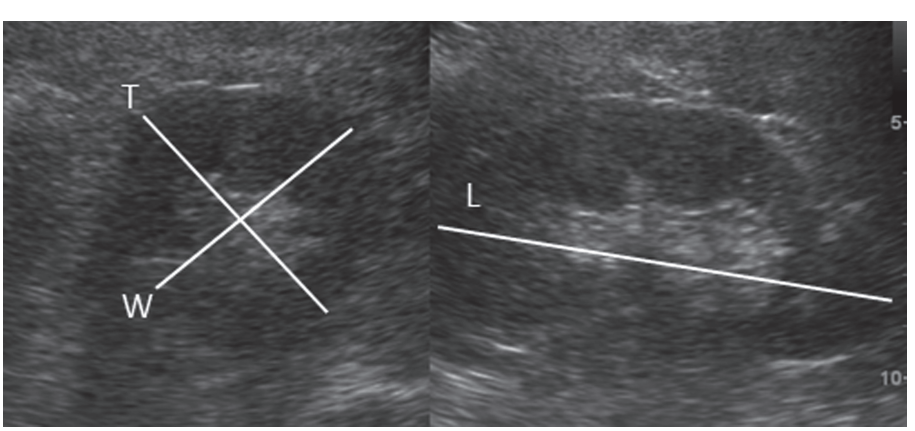


Figure 2 - Measurement of kidney sinus volume on the US image. T indicates thickness, W, width; L, length.

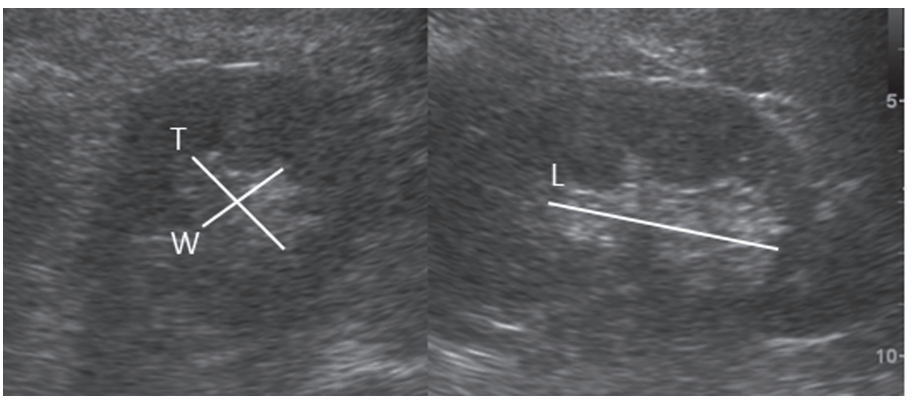
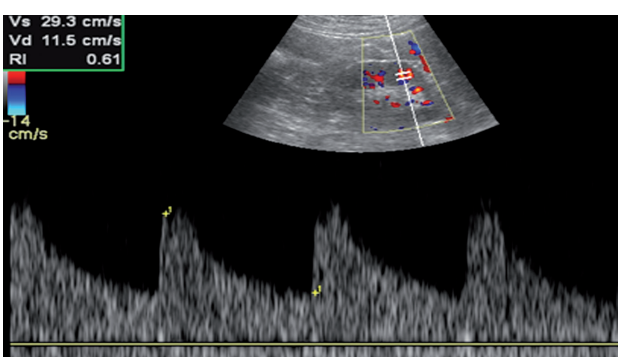


Figure 3 - Doppler waveform and measurement of RI for the intrarenal artery.



kidney volume was significantly larger among males ($p<0.05$). The correlations between patients' kidney dimensions and body parameters are shown in Table-3.

Kidney measurements were correlated with body height and weight. A positive correlation was observed between body height and kidney length and width ($p=0.005$). A significant positive correlation was also observed between body weight and kidney length and width ($p<0.001$). There was no correlation between anteroposterior kidney measurements and body height or weight. A significant correlation with total kidney volume and kidney measurements was determined for body weight in both kidneys ($p<0.001$, r: 0.32-0.44). A strong correlation was found between kidney volume and body weight compared to body height ($p<0.001$, $p<0.05$, respectively, Figure-4). A significant correlation with kidney volume and width was revealed for both kidneys ($p<0.001$, Figure-5). A positive correlation was observed between parenchymal and total kidney volumes for both kidneys ($p<0.001$). Left kidney volume was significantly greater than right ($p<0.05$).

There was no correlation between kidney dimensions and volumes and RI. A negative but insignificant correlation was determined between

Table 1 - Demographic characteristics.

Characteristics	Women	Men	P
Patients	79	73	
Age (yrs)	41±13	44±14	>0.05
Height (cm)	160±7	168±12	<0.001
Weight (kg)	71±12	77±11	<0.005
BMI (kg/m^2)	27±6	28±5	>0.05
RI	0.62±0.08	0.60±0.06	>0.05

RI = Resistivity index, **BMI =** Body mass index

Table 2 - Mean kidney length, volume and RI.

	Women		Men		Total	
Mean ±SD	Right kidney	Left kidney	Right kidney	Left kidney	Right kidney	Left kidney
Length (cm)	102±7.6	101±11.1	105±7.6	107.7±6.9	10.3±7.8	10.4±9
Total volume (cm^3)	151.8±39	159.8±37	164.3±38	175.8±41	158±39	168±40
Parenchymal volume (cm^3)	123.8±32.2	128.5±31.2	129.5±36.8	137.5±38.4	126±34	133±35
RI	0.62±0.08	0.60±0.08	0.63±0.08	0.64±0.07	0.63±0.08	0.62±0.08

RI = Resistivity index

Table 3 - Correlation between patients' kidney dimensions and body parameters.

Body parameter	MKL		MKT		MKW		MKTV		MKPV	
	R	L	R	L	R	L	R	L	R	L
Height	0.23**	0.23**	0.07	0.02	0.23**	0.20*	0.22**	0.15	0.20*	0.10
Weight	0.32**	0.38**	0.28**	0.14	0.23**	0.22**	0.39**	0.35**	0.35**	0.30**
BMI	0.07	0.15	0.09	0.09	0.07	0.04	0.12	0.17*	0.10	0.18*
Age	-0.07	0.05	-0.02	0.07	-0.02	-0.02	-0.03	0.02	-0.08	-0.03

***p<0.05; **p<0.001; MKL =** mean kidney length; MKT = mean kidney thickness; **MKW =** mean kidney width; **MKTV =** mean kidney total volume; **MKPV =** mean kidney parenchymal volume; **R =** Right; **L =** Left; **BMI =** body mass index

kidney dimensions and volumes and age. A weak correlation with left kidney volume was observed for BMI ($p<0.05$, r: 0.20). A mild correlation with parenchymal volume and total volume was observed for BMI for both right and left kidneys ($p<0.05$). However, left kidney volume correlated better with BMI, in contrast to previous studies (4, 4-12). There was no significant correlation between total and parenchymal kidney volumes and RI for either kidney ($p>0.05$). Gender showed the weakest correlation with kidney dimensions ($p<0.05$, r: 0.20-0.23).

DISCUSSION

Kidney length and volume measurements are generally preferred as the basis for decisions concerning renal disease and are regarded as surrogates for renal function. Measurement of kidney volume with US is a simple and noninvasive method (2). Kidney volume is more of an approximation of size than length because the shape of the kidney varies considerably. It is also an excellent indicator of renal function and correlates very well with body indexes (6).

A limited number of studies have measured normal kidney volume using various imaging methods (7, 8). Shin et al. measured volume in the Korean population using multidetector computed tomography (MDCT) (9). The advantage of using MDCT is that the shape of the kidney is irrelevant. However, it is ionizing, potentially nephrotoxic because of the use of contrast media and is not particularly practical. Cheong et al. measured kidney volume and kidney length using magnetic resonance imaging (MRI) (8). However, MRI is expensive and time consuming and is not widely available for daily clinical practice in most countries.

US is the most widely used imaging method for kidney measurements (10). It is cheap,

Figure 4 - Relation between mean kidney volume (cm^3) and body weight (cm).

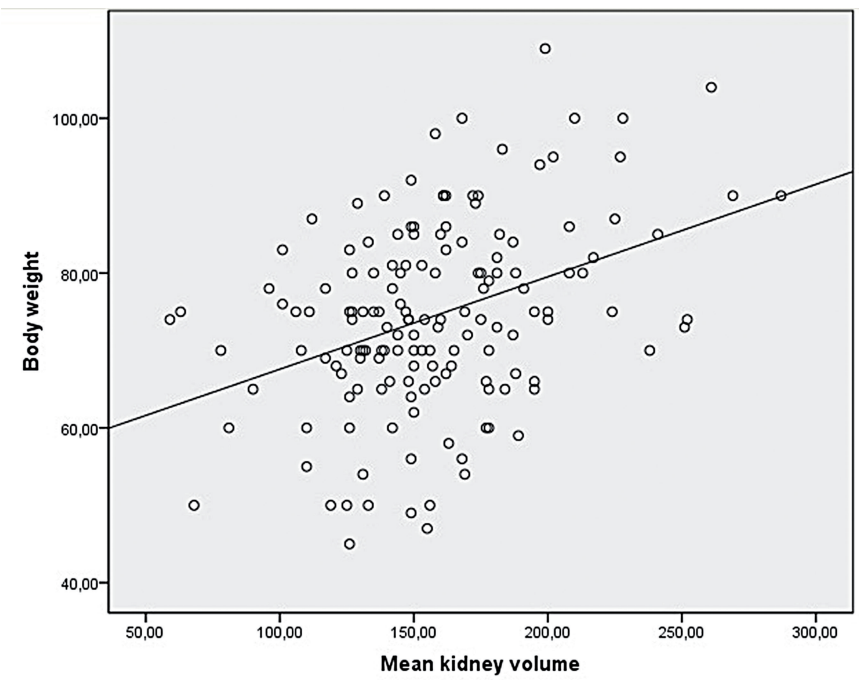
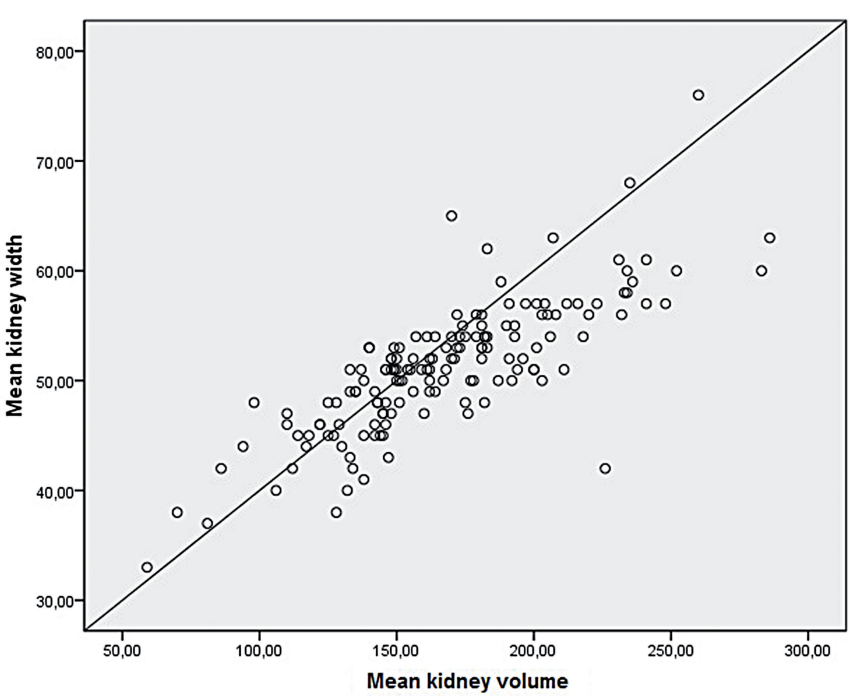


Figure 5 - Relation between mean kidney volume (cm^3) and kidney width (cm).



fast, and easily available. US is useful in renal disease assessment because of its low cost and the short examination time involved. Sonographically, the kidney consists of a central highly echogenic core called the kidney sinus, surrounded by a comparatively less echogenic area called the kidney parenchyma. Total kidney volume comprises both the kidney sinus and the kidney parenchyma. Measurement of kidney dimensions using US was investigated by Dixit et al. (11). In this study we used US to measure kidney volume in a Turkish population.

Mean kidney volume and length of 205.29±36.81 cm^3 and 10.8±0.69 cm, respectively, were reported in a study by Shin et al. They also found that the mean length of the left kidney was greater than that of the right (9). One study reported mean kidney lengths of 11.2 cm on the left and 10.9 cm on the right. It reported mean kidney volumes of 146 cm^3 in the left kidney and 134 cm^3 in the right (12). In this study, mean kidney lengths were 10.3±10 cm for both. Mean volumes of the right and left kidneys were 160.5±39 cm^3 and 168.2±40 cm^3, respectively. Left kidney volume was also significantly greater than right kidney volume. This may be because the spleen is smaller than the liver, so the left kidney has more space for growth. Another possible explanation is that the left renal artery is shorter than the right. Increased blood flow in the left renal artery may therefore cause a relative increase in left kidney volume. Our mean kidney volumes differed slightly from those of other studies. This may possibly be due to differences among ethnic groups.

Studies have reported that both kidney volume and length were significantly correlated with all body indexes (9). Body weight showed the best correlation with right kidney dimensions, whereas BMI and age showed the weakest correlations with body indexes (13). Gavela et al. reported a good correlation between kidney parameters and body parameters, with height exhibiting the best correlation (14). Cheong et al. found no correlation between kidney volume and BMI, height or weight (8). Previous studies have shown that the kidney becomes relatively shorter and thicker with age (15). Kidney size decreasing with age is almost entirely due to parenchymal reduction (12). Some studies have reported that kidneys are larger in males than in females (12, 16).

Our study revealed a significant correlation with kidney volume and width for both kidneys ($p<0.001$). A correlation with total kidney volume and measurements was determined for body weight for both kidneys. Left kidney volume correlated better with BMI than in previous studies (12, 17). A strong correlation was determined between kidney volume and body weight in previous reports, although our study revealed only a very weak correlation between kidney volume and body height. In contrast to previous reports, our results reveal no significant difference between kidney volumes and measurements at any age (9). Mean kidney volume was significantly greater in males. This may be due to the greater body height and weight observed in males.

RI is a parameter which correlates with renal function, and it is logical that RI should increase when renal function decreases. Kidney volume and RI are predictors of renal function and correlate with body indexes (6). Mean RIs for left and right kidneys were 0.60 and 0.62, respectively, in our study. There was no significant correlation between total and parenchymal kidney volume and RI for either kidney ($p<0.05$).

Our study has certain limitations. The main limitation of this study is that US is an operator-dependent technique. In present study, only healthy population was used. Lack of patients of the transplant kidney group or with renal disease also limited the study.

In conclusion, of all the variables assessed in our study, the most significant factors associated with kidney volume are kidney width and body weight for the Turkish population. Because kidney volume is important for renal functional reserve after partial nephrectomy, serial measurements can provide information regarding disease progression or stability. US examination is a feasible method for measurement of kidney volume and it is available on daily clinical practice.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 823-827, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.14

Difference between actual vs. pathology prostate weight in TURP and radical robotic-assisted prostatectomy specimen

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ABSTRACT

Introduction: To investigate and highlight the effect of formaldehyde induced weight reduction in transurethral resection of prostate (TURP) and radical robotically-assisted prostatectomy (RALP) specimen as a result of standard chemical fixation.
Materials and Methods: 51 patients were recruited from January 2013 to June 2013 who either underwent a TURP (n=26) or RALP (n=25). Data was collected prospectively by the operating surgeon who measured the native, unfixed histology specimen directly after operation. The specimens were fixed in 10% Formaldehyde Solution BP and sent to the pathology laboratory where after sufficient fixation period was re-weighed.
Results: Overall mean age 64.78 years, TURP mean age 68.31 years RALP mean age 61.12years. We found that the overall prostatic specimen (n=51) weight loss after fixation was a mean of 11.20% (3.78 grams) ($p \leq 0.0001$). Subgroup analysis of the native TURP chips mean weight was 16.15 grams and formalin treated mean weight was 14.00 grams ($p \leq 0.0001$). Therefore, TURP chips had a mean of 13.32 % (2.15 grams) weight loss during chemical fixation. RALP subgroup unfixed specimen mean weight was 52.08 grams and formalin treated mean weight was 42.60 grams ($p \leq 0.0001$), a 19.32 % (9.48grams) mean weight reduction.
Conclusion: It has not been known that prostatic chips and whole human radical prostatectomy specimen undergo a significant weight reduction. The practical significance of the accurate prostate weight in patient management may be limited, however, it is agreed that this should be recorded correctly, as data is potential interest for research purposes and vital for precise documentation.

ARTICLE INFO

Key words:
Prostatectomy; Transurethral Resection of Prostate; Pathology; Prostate; Robotics; Prostatectomy

Int Braz J Urol. 2014; 40: 823-7

Submitted for publication:
January 07, 2014

Accepted after revision:
May 13, 2014

INTRODUCTION

Formalin is the most commonly used chemical for tissue fixation worldwide as it provides excellent morphological preservation for routine histology (1). Formaldehyde fixation preserves tissue from degradation, and maintains the structure of the cell and of sub-cellular components such as cell organelles (e.g., nucleus, endoplasmic reticulum, mitochondria). Mainly 10% neutral buffered formalin (4% formaldehyde) is being used for light microscopy. (1).

Its chemical action in order to preserve tissue is exerted mainly by irreversibly cross-linking protein. The main action of these formaldehyde fixatives is to cross-link amino groups in proteins through the formation of methylene bridges ($-CH_2-$), in the case of formaldehyde, or by a C5H10 cross-links in the case of glutaraldehyde. Formaldehyde will cause a significant amount of prostate tissue shrinkage by 4.1-4.5%, however we cannot find any scientifically valid result available regarding weight loss resulting by chemical fixation in prostatic specimens (2,3).

Previous studies were conducted in animal organs (4) to estimate the effect of storage in formalin on organ weights; however, we can not find comparative papers for human prostate even after an extensive literature search.

Measurement of prostate weight can be determined by transabdominal (TAUS) or transrectal ultrasound (TRUS) (5), however increasingly magnetic resonance imaging (MRI) (6, 7) and multiparametric MRI are used mainly in oncology setting to obtain more precise and accurate estimation of prostate size for treatment plan. In terms of the prostate size/volume a large 67 TURP (transurethral resection of the prostate) series was analyzed by Mayer et al. (8) which showed a mean pre-operative prostate volume of 47.6 grams, with mean resected prostate tissue of 25.8 grams. In a single center prospective study published by Badani et al (9), 2766 RALP (robotic-assisted laparoscopic prostatectomy) results showed a mean prostate weight of 49.91 grams (13-220 grams); preoperative weight was not recorded. Generally none of these or other trials recorded when and how is prostatic specimen weight recorded, which could carry a significant bias due to chemical fixation induced weight loss.

Our aim was to quantitatively evaluate the discrepancies in actual versus post formaldehyde-fixed prostate weight in our TURP and RALP specimens involving the influence of formalin fixation.

MATERIAL AND METHODS

Fifty-one patients were recruited prospectively between January 2013 to June 2013 who either underwent a TURP (standard monopolar resection) (n=26) for bladder outflow obstruction (BOO) or a RALP (n=25) for histologically proven organ confined prostate cancer in our institution. RALP specimens were measured en block with the seminal vesicles. Data was collected for initial measurement of the native, unfixed histology specimen directly after the operation by the operating surgeon and measured without delay on a SECA 856 digital medical scale (Graduation Weight: 1 g < 3 kg > 2 g). Weight of the specimen was recorded by the research team on an encrypted pen drive with no access but to the research team. Pathologists were unaware of the original specimen weight measured by the research team. Specimens were fixed in formaldehyde solution BP 10% v/v (equivalent to 4% formaldehyde) with sodium chloride BP 0.9% w/v. and sent to the pathology laboratory where after sufficient period of fixation were measured on OHAUS EB3 series scale (Graduation Weight: 1 g < 3 kg > 1 g). Standard 1-2-5-10-100 grams test weights were used to compare accuracy of the scales to avoid bias from measurement. Both scales measured tester's weight precisely and accurately with no difference in terms of weight. Overall and subgroup analysis of the native untreated prostate weights and chemically treated prostate weights were analyzed with paired t-test.

RESULTS

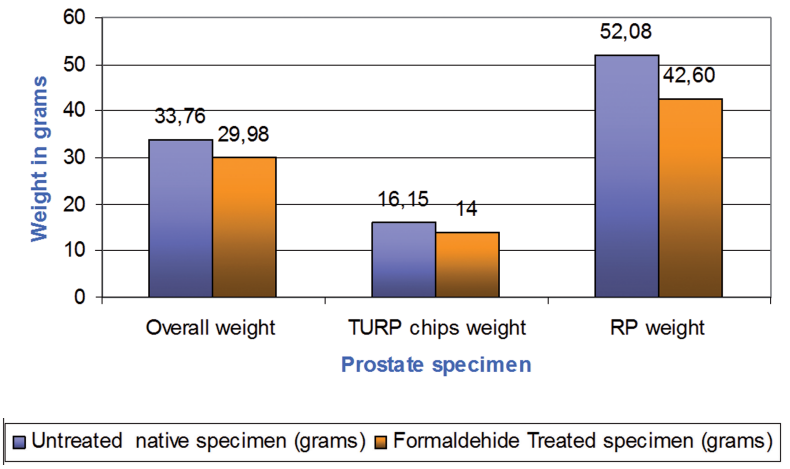
A total number of 51 patient were recruited, TURP (n=26) and RALP (n=25) over six months (from January 2013 to June 2013). Demographical characteristics of the patients showed an overall patients' mean age of 64.78 (SD±8.43), TURP patients' mean age of 68.31 (SD±9.43), RALP patients' mean age of 61.12 (SD±5.29).

Overall native specimen (n=51) mean weight was 33.76 grams (SD±22.22) and formaldehyde treated mean weight was 29.98 grams (SD±20.56), a difference which is extremely statistically significant ($p \leq 0.0001$), with a standard error of 0.472 (Figure-1). The mean weight reduction after chemical fixation was 11.20% compared to native prostatic tissue weight.

Subgroup analysis of native TURP chips showed a mean weight of 16.15 grams (SD±9.01) and formaldehyde treated mean weight of 14.00 grams (SD±8.76) a difference which is extremely statistically significant ($p \leq 0.0001$), with a standard error of 0.46, The mean weight reduction after chemical fixation was 13.32% compared to native TURP chips weight.

RALP native specimens mean weight was 52.08 grams (SD±16.09) and formaldehyde treated mean weight of 42.60 grams (SD±15.36) a difference which is extremely statistically significant ($p \leq 0.0001$), with a standard error of 0.696.

Figure 1 - Mean weight of the native and the post formaldehyde fixed specimen subgroups in grams. (Overall, TURP chips and RALP)



Mean weight reduction of the RALP specimens was 19.32 % after chemical fixation.

Overall final histology mean reporting time was 7.24 days (SD±3.43). TURP specimen final histology mean reporting time was 6.15 days (SD±3.86) and 8.36 days (SD±2.51) for the RALP specimen which was slightly longer (reporting days include weekends as well).

None of the TURP chips contained incidental adenocarcinoma on the final histology report, and all were reported as a benign prostatic hyperplasia (BPH) or adenofibromyomatous hyperplasia.

DISCUSSION

A large 67 TURP series was analyzed by Mayer et al. (8) which showed a mean pre-operative prostate volume of 47.6 grams, mean resected prostate tissue 25.8 grams with a resection time of 38.5 minutes. In a single center prospective study published by Badani et al (9) 2766 RALP results showed a mean prostate weight of 49.91grams (13-220 grams), with a mean operative time of 154 minutes, preoperative prostate volume was not included. Our data correlates well in terms of the average prostate volume/weight around 45-50 grams in these studies, however none of these studies nor other articles specify precisely how and when the specimen was weighed.

In a common clinical setting, transabdominal (TAUS) or transrectal ultrasound (TRUS) (10) can be used to assess prostate size. There have been studies working on the correlation of TAUS and TRUS in the prostate volume measurement (5, 11) which suggest a good correlation between transabdominal estimation of prostatic volume with the transrectal method. Other studies showed (12) that prostatic weight and volume measured with TAUS are overestimated in about 50% of cases, therefore suggested that TRUS shall remain the gold standard to monitor prostate volume and weight. With the evolution of imaging technology, magnetic resonance imaging (MRI) (6, 7) and multiparametric MRI and MR- positron emission tomography (PET) that offer detailed images of the prostate could potentially offer more precise and accurate estimation of prostate size.

Accurate reporting of radical prostatectomy specimens is becoming more important as we gain insights into how cancer therapy should be tailored according to risk categories, therefore handling of these specimens must be standardized, enabling the correct identification of histopathological risk factors for poor outcome (13). When tumor and or prostatic tissue volume is measured planimetrically, results are multiplied by a

correction factor to compensate for tissue shrinkage caused by processing the specimen (3). As previously reported by Jonmarker et al, the tissue shrinkage after fixation with formalin in radical prostatectomy specimen resulted in an average linear shrinkage of 4.5% corresponding to a volume correction factor of 1.15 (2).

As well as volume/size, the weight of the prostatic specimen has also gained attention lately as Peiguo et al showed a relationship with low median prostate weight (49g) resulting in a significantly higher positive margin rate and incidence of extraprostatic extension (14) in a large prospective study of a laparoscopic radical prostatectomy series. In their study it was 1.523 times more likely to have positive margins with small weight prostates. We found that our RALP specimens had 6% more mean weight loss (19.32% vs. 13.32%) than TURP chips.

Limitations of our study are the fact that two different types of scale were used, however both scales measured tester's weight precisely and accurately with no difference in terms of weight. A potential source of bias for our data could be the fact that the RALP prostate specimens were weighed with the seminal vesicles attached, however, they were weighed again by the pathologist exactly the same way. The true weight of the prostate gland can only be determined if the seminal vesicles are detached from the prostate gland before weighing and that was recommended by the International Society of Urological Pathology (ISUP) Consensus Conference (15). They also concluded that 76% of participants weighed the prostate with the seminal vesicles attached and it was noted that some urologists request the weight of the entire specimen in order to assign a level of difficulty to the surgical procedure, in which case the weights of the prostate and the seminal vesicles could be combined (15).

Therefore we cannot determine the weight loss of the seminal vesicle as a result of formaldehyde fixation, and we cannot predict how that affected our overall RALP specimen results. On the contrary, detaching the seminal vesicle in theatre could potentially carry a hazard of damaging prostatic and seminal vesicle margins resulting in understaging of the disease (16), therefore the author would not recommend it to be performed by the urologist. Further evaluation is needed to determine the formaldehyde induced seminal vesicle weight loss and shrinkage.

CONCLUSIONS

Chemical fixation performed with formaldehyde causes a considerable amount of tissue shrinkage; however it has not been known that prostatic chips and whole human radical prostatectomy specimens undergo a significant weight reduction as well. The practical significance of the accurate prostate weight in patient management may be limited, however it is agreed by everyone that this should be recorded, as such data are of potential interest for research purposes and vital for precise documentation. Generally, most of the articles quote the histologically reported prostate weight which is biased by chemical fixation at least 10%-20% reduction according to our study findings. These facts raise serious concerns about the accuracy of the previous studies dealing with prostatic specimen weight. The urological and pathological community will have to raise the awareness on chemical fixation induced specimen weight loss and have to reach consensus in order to avoid measurement bias and hence precise weighing which will lead to a clear and accurate data.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 828-834, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.15

Efficacy of Pelvisoft® Biomesh for cystocele repair: assessment of long-term results

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ABSTRACT

Introduction and Hypothesis: To our knowledge a study regarding the efficacy of Pelvisoft® Biomesh for cystocele repair has not previously been reported in the literature. The aim of our study was to assess the long-term efficacy, subjective outcomes and complications in the use of a non-synthetic porcine skin mesh graft (Pelvisoft® Biomesh) associated with transvaginal anterior colporrhaphy in the treatment of cystocele prolapse.

Materials and Methods: A retrospective study was performed at a single centre. Thirty--three women aged 35-77 years underwent cystocele repair using Pelvisoft® graft between December 2005 and June 2009. Twenty-nine women who underwent transvaginal cystocele repair with Pelvisoft® Biomesh for over a 2 years period were assessed. Four patients were lost to follow-up. Cystocele repair was performed via the vaginal route using Pelvisoft®Biomesh implant by inserting it in the anterior vaginal wall.

Results: The median follow-up time was 54.0 months. The rate of recurrence was 17.3%. A total of 6.9% of patients presented early mesh exposure treated by conservative treatment. The mean PFDI-20 score was 72.2. Among sexually active women, the mean PISQ 12 was 33.9 but 56.2% had dyspareunia. After surgery, 6 patients had de novo intercourse.

Conclusions: Our results show that the use of Pelvisoft® biomaterial associated with anterior colporrhaphy for cystocele repair appears to be safe with acceptable failure and complication rates at long term. Nevertheless, an adverse impact on sexual function was reported by the majority of patients.

ARTICLE INFO

Key words:
Cystocele; Biocompatible Materials; Prolapse

Int Braz J Urol. 2014; 40: 828-34

Submitted for publication:
January 13, 2014

Accepted after revision:
May 03, 2014

INTRODUCTION

Pelvic organ prolapse is characterized by a descent of the pelvic organs into the vaginal wall. The most frequent occurrence is anterior vaginal wall prolapse or cystocele (1). It is a major health--care problem that affects about 40% of women over 50 (1). According to Olsen et al. approximately 11% of women will undergo reparative surgery for prolapse or stress urinary incontinence (SUI) and a second operation is estimate to be required in 29.2 % of cases (2). Furthermore, 17% of women who undergo pelvic organ prolapse (POP) or SUI surgery may require re-operation in 10 years time (3). When conservative treatment has failed, surgery is the treatment of choice for women with symptomatic cystocele. Trans-vaginal cystocele repair by anterior colporrhaphy is associated with a high rate of failure reaching 40% or higher (4-6). In order to decrease this high recurrence rate, the use of meshes (synthetic polypropylene or non--synthetic biological materials) has been used to

repair POP during the past decade. Polypropylene monofilament and macroporous tissue is the most widely used. This material assures good anatomical repair, at short and median term, although there is a high rate of adverse events i.e. vaginal erosion, dyspareunia or pelvic pain. The use of biological biomaterials appears to have a lower complication rate, however few evaluations have been reported and most of them with short term follow-up. The aim of our study was to assess the long-term efficacy, subjective outcomes and complications in the use of a non synthetic porcine skin mesh graft (Pelvisoft® Biomesh) associated with transvaginal anterior colporrhaphy in the treatment of cystocele prolapse.

MATERIALS AND METHODS

Study population

Thirty-three women who underwent transvaginal cystocele repair with implantation of Pelvisoft®, from December 2005 to June 2009, were included in a retrospective study. Two experienced surgeons performed the repair surgery. Pre-operative urogynaecological examination was carried out with patients in the dorsal lithotomy position. Tests included a speculum valve examination, a cough test and Valsalva manoeuvre. The degree of prolapse was defined according to the POP-Q classification (7). All patients had a cystocele stage >1 with or without associated apical or posterior vaginal wall prolapse. Urodynamics, including flow rate measurement, urethrocystometry and profilometry were performed prior to cystocele repair if there were concurrent voiding abnormalities. All patients had a follow-up consultation at 2 months after surgery. Then, two years or more after surgery, all patients were examined by an independent blinded urologist and prolapse recurrence was defined as vaginal descent of the anterior wall POP-Q stage >1.

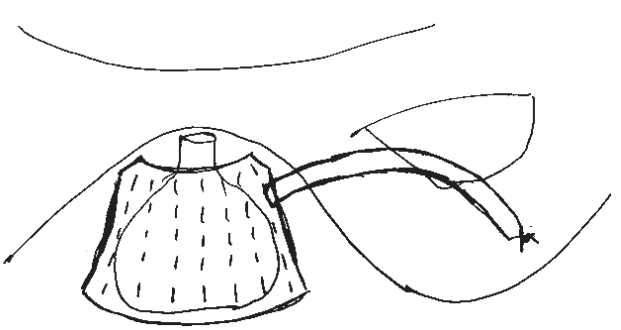
At each patient consultation, a questionnaire regarding subjective satisfaction to assess sexuality was completed. The French validated translation of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) was used to assess the effects on sexual function (8) with a score range from 0 to 48, the higher score indicating better sexual function. The study was not submitted for Ethics Committee approval because this is standard clinical practice study with no randomization. The French validated translation of Pelvic Floor Distress Inventory (PFDI-20) evaluated pelvic floor disorders (9). It consists of 3 subscales: the pelvic organ prolapsed distress inventory (POPDI-6), the urinary distress inventory (UDI-6), and the colo-rectal-anal distress inventory (CRADI-8) The response of each item was rated from 0 to 4. The mean value of all of the answered items within the corresponding scale was then multiplied by 25. Each subscale ranges from 0 to 100, with a maximum summary score of 300.

Surgical technique

Pelvisoft® Biomesh (C.R. Bard, Cranston, R.I.,) is a macroporous mesh material used for cystocele repair. It is a porcine dermal acellular matrix collagen biomesh consisting of fibrous, acellular collagen and elastin fibres. A 4 X 7cm size was used for the study. All women had negative urine culture before surgery and received prophylactic antibiotics (i.e. cefazoline) during surgery.

Initially an anterior colpotomy was performed with a dissection of the bladder from the vagina, opening the pelvis fascia on each side. The implant was inserted transversally over the bladder and attached with 3-0 monofilament polyglactin absorbable sutures on the median line proximal to the periurethral tissue and distal to the cervical ring. On each side, the implant was attached (Figure-1) with a 0 monofilament polypropylene transobturator non-absorbable suture, using a Hemet

Figure 1 – Lateral mesh fixation.



The prolene suture node is at the upper right part of the subcutaneous tissue. A transobturator route is used with a Hemet needle stitched from the outside to the inside.

needle back and forth. The colpotomy was sutured with a non interrupted 0 monofilament polyglactin. A vaginal pack and a Foley catheter were left indwelling for 24h.

An associated apical or posterior prolapse was treated respectively either by sacrospinous suspension or a posterior colporrhaphy. When preoperative SUI was associated, a transobturator tape (TOT) polypropylene sling procedure was performed. A hysterectomy was performed if associated with ≥2 uterus prolapse.

Statistical analysis

Values were reported at the mean plus or minus standard deviation (SD) or at the median and interquartile range (IQRs). Quantitative variables were analyzed using the Mann-Whitney test. For qualitative variables, Fisher's exact test was used. A $p<0.05$ was considered to be statistically significant. Statistical analyses were performed with GraphPad Prism (version 5.01 for Windows).

RESULTS

Of the 33 patients who underwent cystocele repair, four patients were lost to follow-up. Patient's characteristics and prolapse staging are shown in Table-1.

Characteristics of surgery and early complications are listed in Table-2. The median duration of surgery was 58.0 min (IQR: 45.0-90.0), including all operative procedures. No per-operative complication was observed, except for a post-voiding residual in three patients (>150mL). Resolution occurred in all cases after intermittent self-catheterization. One patient presented a vaginal haematoma treated surgically. Two patients had early mesh exposure due to surgical dehiscence in the anterior wall which resolved conservatively and no recurrence occurred. These cases were associated with a vaginal hysterectomy. Urinary tract infection was treated by antibiotics. Mean hospital stay was 3.7 days (SD: 1.0).

Median follow-up period was 54.0 months (IQR: 37.0-57.0, range: 27.0-65.0). Pre and post-operative anatomical findings are shown in Table-3. Of the 29 patients, five of them had a cystocele recurrence. At follow-up, among patients with recurrent prolapse, two had an early recurrence and had previously undergone laparoscopic sacral fixation. The recurrence rate was not statistically different in patients with or without an apical defect or rectocele repair (p=0.6). Median time to recurrence was 33.0 months (IQR: 10.5-49.0. range: 10.0-58.0).

Table 1 – Patients characteristics.

Characteristics	Patients (n=29)
Age, year, mean, (SD)	61.31 (12.01)
BMI, kg/m², mean (SD)	26.09 (4.47)
Surgical History, No (%):	
Prolapse repair	8 (27.6)
Suburethral sling	4 (13.8)
Hysterectomy	11 (37.9)
Intra vaginal surgery	9 (31.0)
Voiding abnormalities, No (%):	
Urgentury	10 (34.5)
SUI	14 (48.3)
Voiding difficulties	7 (24.1)
Constipation, No (%)	10 (34.5)
Anal incontinence, No (%)	3 (10.3)
Prolapse staging, No (%):	
Cystocele: First degree	0 (0.0)
Second degree	21 (72.4)
Third degree	8 (27.6)
Rectocele: First degree	7 (24.1)
Second degree	4 (13.8)
Third degree	0 (0.0)
Uterine/vaginal vault prolapse: First degree	2 (6.9)
Second degree	5 (17.2)
Third degree	1 (3.4)

BMI = body mass index.
SUI = stress urinary incontinence.

Table 2 – Characteristics of the surgery.

Characteristics	Patients, No. (%)
Concomitant procedure	
Vaginal hysterectomy	6 (20.7)
Posterior colporrhaphy	9 (31)
Suburethral sling	11 (37.9)
Uterine/Vaginal vault suspension	5 (17.2)
Post-operative complication	
Acute urine retention	3 (10.3)
Haematoma	1 (3.4)
Urinary tract infection	1 (3.4)
Mesh exposures	2 (6.9)

Table 3 – Anatomical outcomes.

	Pre-operative stage of cystocele, No. (%)	Post-operative stage of cystocele, No. (%)
Grade 0	0 (0)	15 (51.7)
Grade I	0 (0)	10 (34.4)
Grade II	21 (72.0)	3 (10.3)
Grade III	8 (28.0)	1 (3.4)
Grade IV	0 (0)	0 (0)

A de novo SUI occurred in 24.1% and de novo urgency in 13.7%. Urgency was resolved in 50.0%.

Our retrospective study regarding sexuality showed that 10 women still experienced sexual intercourse before surgery, with dyspareunia in 40.0 % of cases. After surgery, 16 patients had a sexual life showing an improvement in sexuality with 6 patients who had de novo sexual intercourse. The mean PISQ-12 score was 33.9 (SD: 8.7). The PISQ-12 showed that among women who had intercourse (16 patients), nine had pain during sexual activity. The mean PFDI-20 score was 72.2 (±61.7) (Table-4). It was significantly higher in patients with recurrence ($p<0.05$). Recurrence was associated with an adverse impact in quality of life, prolapse distress, colo-rectal and anal distress ($p<0.05$).

Table 4 – PFDI-20 Scores (recurrence vs no recurrence).

PFDI-20	Recurrence (n=3)	No recurrence (n=26)	p value
Total	174.9 (6.2)	60.3 (53.4)	0.009$^{\Delta}$
POPDI-6	52.7 (31.3)	14.2 (14.1)	0.033$^{\Delta}$
CRADI-8	57.3 (31.6)	19.7 (17.4)	0.024$^{\Delta}$
UDI-6	65.3 (4.8)	26.4 (8.9)	0.078$^{\Delta}$

Mann and Whitney Test: Δ

DISCUSSION

To our knowledge, our study is the first to evaluate outcomes of Pelvisoft® non synthetic biomaterials in cystocele treatment.

In the treatment of POP, the search for the "ideal graft" remains problematic. Currently, the most widely used material is macroporous low weight polypropylene. Synthetic meshes provide satisfactory anatomical results but side-effects and tolerance still remain a major concern. Therefore, studies regarding non-synthetic biomaterials are limited. Non-synthetic biomaterials have been reported to have a better biocompatibility and fewer side effects. As previously mentioned, Pelvisoft® biomesh, used in our study, is an acellular collagen matrix for tissue repair. Using a rat model, Konstantinovic et al. showed that there was no shrinkage of Pelvisoft® after a 90 day period although an increase in size of 17% has been observed (10). Macropores present in the material facilitate the integration of the implant into the surrounding tissue and provide a better resistance (11). In fact, in contrast with Pelvicol®, another porcine dermal collagen implant (not macroperforated), the pores in Pelvisoft® permit new vessel generation as well as a better tensile strength (12). The tensile strength of Pelvisoft® is also similar to that of polypropylene (12). Fenestrations in the graft permit immediate contact between the vaginal mucosa and underlying host tissues and may improve long-term functional outcome. Moreover, in the absence of

pores, it can form a mesh encapsulation due to fibrotic tissue and allow dead space formation between native tissue and the graft. To date, only one clinical study has been reported in the literature assessing the properties of Pelvisoft® for rectocele repair. In a series of 35 patients, Dell et al. have shown that the use of these materials led to good anatomical results with sexual activity preservation (13). These authors observed that no graft exposure occurred due to fenestration.

In our study using Pelvisoft®, the recurrence rate was 17.2% and is less than the 40% reported with native-tissue colporrhaphy repair without mesh (4-6). However, this rate is higher than that reported with the use of polypropylene mesh. In recent prospective studies using synthetic meshes, the recurrence rate varies from 9.0% to 10.2% with a median follow-up of 12 months (14, 15). The incidence of cystocele recurrence increased over time with the follow-up. A 24.0% recurrence rate with 79 months follow-up was reported by Letouzey et al. (16). Two recent randomized trials have reported better results with a failure rate of 5.7% and 13% respectively for a follow-up of 24 to 60 months (5, 17). However, in these two studies the major concern was a mesh exposure rate of 11.1% and 19%. Vaginal mesh extrusions appear to be the most common complication observed with the use of a synthetic mesh graft and its management is often surgical. In the literature, with a follow-up higher or equal to 1 year, reported mesh-exposure was 4.0 to 14.4% (14-16). Two different processes may be involved. Early exposure could be caused by a healing defect resulting of the procedure. A late exposure may be a rejection phenomenon due to chronic tissue erosion depending on the material used (18). In our study, two patients presented early mesh exposure in the 15 days following surgery which was related to procedure (dehiscence of healing). They underwent concomitant hysterectomy which is a reported risk factor of exposure (19). However, we did not observe any late exposure. The hypothesis that may explain this result is that Pelvisoft® is composed of acellular collagen matrix which had minimal immunologic and inflammatory reaction compared to synthetic materials. The risk of mesh exposure could also result due to the friction during intercourse (18). Our rate of women sexually active was low which may explain our good results on late exposure. Furthermore, among the women who had sexual intercourse, dyspareunia might have been a protective factor since pain can lead patients to avoid sexual intercourse. In fact, in our population 56.2% had dyspareunia. Moreover, the use of a synthetic mesh may lead to its shrinkage and consequently responsible for vaginal shortening and tightening. This may explain the better impact of surgery on quality of life and sexuality with Pelvicol® (biological graft) than with Gynemesh PS® (non absorbable mesh) observed in Natale et al. study (20). In our study, during follow-up, elasticity of the vagina was normal, with no shortening.

Some studies using other porcine dermis mesh have reported a low recurrence rates. Meschia et al. in a series of 201 women observed the lowest recurrence rate in the treatment of cystocele with Pelvicol® (7%) at 1 year follow-up, in comparison to patients treated with colporrhaphy (20 %) (21). Gomelsky et al. studied 70 patients over a 24 months period treated with Pelvicol® for POP and reported a 12.9% recurrence rate (22). In a retrospective study of 119 patients, Handel et al. compared anterior colporrhaphy, polypropylene meshes and porcine dermis meshes in cystocele repair with a 13.5 months mean follow-up (23). With the use of the porcine dermis graft, recurrence and erosion rates were 36% and 21% respectively, and this was significantly higher than in the two other groups. Two additional studies using Pelvicol® showed a high rate of recurrence: Dahlgren et al. reported a 58% recurrence at 3 years follow-up, while Natale et al. reported a 43.6% recurrence rate at 24 months follow-up (20, 24). These high recurrence rates can be explained due to the non-macroporous cross-linked structure of Pelvicol® which decreases strength and durability of tissue support owing to the limitation of neovascularization and encapsulation of the graft (20). Our lower failure rate may have been due to macroperforations in the Pelvisoft® graft which allows a better incorporation of native tissue in grafts than the non macroperforated meshes.

The de novo SUI rate is higher than usually reported in 6 to 12% of patients (5, 6). POP has an adverse effect on the functional quality of

life. Most women avoid sexual activity because of the presence of vaginal bulging (45.3-52.6%) (25). Surgery is an alternative which may improve sexuality; however, some vaginal functions might be altered. Also, the effect of surgery on sexual function remains contradictory. In our study, the impact on sexuality was not evaluated prospectively before surgery but based on a retrospective interview and compared to sexual activity after surgery at the follow-up visit. Our mean PISQ 12 score was 33.9, which was similar to that reported in the literature, i.e. 34.1 to 35.5 (25, 26). Our rate of inactive sexual patients after surgery was 44.8%. Two prospective studies with validated questionnaires showed an improvement of sexual function even if pain had been reported during intercourse after surgery for POP (27, 28), however the mean age of population was relatively young (36 and 51 years respectively). In other studies, sexual function was unchanged regardless of surgical procedure, with or without meshes or via the abdominal route (26, 29). A negative impact of the vaginal route on sexual function was described by Hellstrom and Nilsson, caused by a decreased elasticity of the vaginal wall and disturbance of the female erectile reflex (30). In our study, we observed a high rate of dyspareunia (56.2%) in comparison to other studies, (25, 26, 29), but the responsibility of Pelvisoft® seems to be less, since 40% of sexually active patients had already dyspareunia before the surgery. Further, we could not establish a de novo dyspareunia rate due to the absence of pre-operative evaluation. As regards, overall sexual satisfaction is difficult to evaluate due to a wide range of factors, i.e. age of two partners, widowhood, erectile dysfunction, however surgery seems to have only a limited impact.

CONCLUSIONS

This retrospective study on the use of Pelvisoft® in vaginal cystocele repair reassures this mesh as an interesting option. Our median 54 months follow-up showed positive functional outcomes with non recurrence of cystocele in 82% of patients. However, a long follow-up with a larger patient population is necessary, as well as future randomised controlled trials comparing non synthetic and synthetic meshes.

ABBREVIATIONS

SUI = Stress urinary incontinence
POP = Pelvic organ prolapsed
PISQ-12 = Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire
SD = Standard deviation
IQRs = Median and interquartile range
TOT = Transobturator tape

ACKNOWLEDGEMENT

The authors are grateful to Richard Medeiros, Medical Editor, Medical Editing International for editing the manuscript.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 835-841, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.16

Activity and safety of sunitinib in poor risk metastatic renal cell carcinoma patients

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ABSTRACT

Purpose: To assess the activity, safety and treatment patterns of sunitinib in patients with poor-risk metastatic renal cell carcinoma (mRCC).
Materials and Methods: We retrospectively reviewed the charts of poor risk patients treated with sunitinib from October 2006 to July 2013 who met the eligibility criteria. The primary endpoint was overall survival (OS). Tumor radiological response was measured according to RECIST 1.1 and adverse events (AEs) were assessed through standard criteria.
Results: Median OS was 8.16 months (95% CI, 5.73-10.59). Of the 53 patients included in this analysis, 9 (17.0%) achieved partial response, 12 (22.6%) had stable disease. Median treatment duration was 3.30 months (95% CI: 1.96-4.63) and 26.4% of patients discontinued treatment due to toxicity. Grade 3 or higher AEs occurred in 39.6% of patients, the most common being fatigue (15.1%), neutropenia (9.5%), nausea, vomiting and diarrhea (7.5% each).
Discussion: Sunitinib may benefit some unselected poor-risk patients, although the rates of AEs and drug discontinuation suggest a need for careful patient monitoring.

ARTICLE INFO

Key words:
sunitinib [Supplementary Concept]; Carcinoma, Renal Cell; Safety;

Int Braz J Urol. 2014; 40: 835-41

Submitted for publication:
February 05, 2014

Accepted after revision:
May 03, 2014

INTRODUCTION

Over the past few years, several new agents have been granted approval for the first-line treatment of metastatic renal cell carcinoma (mRCC). These agents include inhibitors of the vascular endothelial growth factor (VEGF) pathway (sunitinib, pazopanib, bevacizumab) and inhibitors of the mammalian target of rapamycin (mTOR) pathway (temsirolimus) (1).

With the exception of the trial investigating temsirolimus (2), pivotal large randomized phase III clinical trials supporting the use of these medications in mRCC excluded or underrepresented patients with poor risk features. However, the efficacy and safety of targeted therapies such as sunitinib in this population is less clear (3). Recently published data suggests that at least 30% of mRCC patients receiving VEGF pathway inhibitors belong to the poor-risk group based on the International Database Consortium (IDC) prognostic model (4). Therefore, we performed a retrospective analysis to evaluate the efficacy, safety and treatment patterns of sunitinib in a non-selected population of poor-risk mRCC patients.

MATERIALS AND METHODS

Study design and population

This study was a retrospective analysis of metastatic RCC patients' electronic charts. All patients were treated with sunitinib at two major cancer centers located in the city of São Paulo, Brazil (Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo and Centro de Oncologia, Hospital Sirio-Libanês), between October 2009 and July 2013. Patients were identified from the hospitals' administrative databases, and relevant information was retrieved from electronic medical records. This analysis was approved by the Institutional Review Boards of both institutions.

The primary study objective was to determine the population's overall survival (OS). Secondary objectives were the following: examination of the safety profiles, frequency of treatment modifications, time to treatment discontinuation and response rate in an outside clinical trial setting.

The patient inclusion criteria were (a) diagnosis of metastatic RCC of any histologic type; (b) poor risk features according to the IDC model (4); (c) a Karnofsky performance status (KPS) of 60 or more at baseline assessment and (d) anti-VEGF--naïve patients before starting sunitinib.

Assessment

Trained physicians extracted patients treatment data from electronic medical records, including the following information: date of RCC diagnosis, demographic variables, comorbidities, metastatic site(s), baseline KPS, drug-related AE data, laboratory data, and the results of key radiological tests. Additionally, the first and last dates of sunitinib use, treatment modifications, and both baseline and follow-up tumor measurements were also recorded. A patient's observation period began on the date of initiation of sunitinib and ended either at the time of their last center visit or death.

Outcome Definitions

Safety

Safety outcomes included the numbers and proportion of patients who experienced specific adverse events (AE), of any grade and of grade 3 or higher. We retrospectively assessed AE and assigned grade levels based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, at chart abstraction because grade levels of adverse events are not regularly recorded in medical charts in clinical settings (5).

Treatment Patterns

Treatment patterns included the numbers and proportion of patients who discontinued treatment or had dose modifications during sunitinib treatment and those who switched to a second-line treatment. The type, date, and the reasons for treatment modification were obtained from the patients' medical charts. Time to treatment discontinuation (TTD) was defined as the time from starting sunitinib to the date of the last administered dose independent of cause for discontinuation or loss to follow-up, whichever occurred first.

Efficacy

Overall survival was defined as the interval between the start of therapy and death from any cause (with survival times censored at last follow-up for patients alive at the time of last assessment). The response assessment was reviewed by an independent radiologist, using guidelines for change in the sum of maximal diameters as defined by Response Evaluation Criteria In Solid Tumors, but responses were not confirmed by a second assessment (6).

Statistical analysis

The patient baseline characteristics, overall response rate (ORR), AEs and sunitinib treatment patterns were reported based on descriptive statistics. Means, medians and ranges were used to describe continuous variables, and frequencies or percentages were used for categorical variables. TTD and OS were estimated by the Kaplan-Meier method, and their 95% confidence interval (CI) were calculated. All data analyses were conducted using SPSS, version 21.0, Armonk, NY.

RESULTS

Patients

Fifty-three eligible patients were identified. Patients' demographic and clinical characteristics are shown in Table-1. The median age was 61.6 years (range 31.2-89.6). The proportion of patients with 3, 4, and 5 adverse prognosis factors were 62.3%, 18.9% and 18.9%, respectively. Most patients were male (71.7%) and had clear-cell histology (90.6%) with no previous systemic treatment (88.7%). As expected, other common poor prognosis features were found in the population. These features included KPS of ≤70 (52.8%), no previous nephrectomy (43.4%) and three or more metastatic sites at baseline (45.3%) (Table-1). The most prevalent metastatic sites were the lungs (75.5%), followed by lymph nodal involvement (47.2%).

Table 1 - Patient characteristics.

Characteristics	Number of patients (n = 53)
Age (years)	
median (range)	61.6 (31.2-89.6)
Sex, n (%)	
Male	38 (71.7%)
Female	15 (28.3%)
KPS, n (%)	
≥80	25 (47.2%)
60-70	28 (52.8%)
Histology, n (%)	
Clear cell	48 (90.6%)
Other	5 (9.4%)
Previous nephrectomy, n (%)	
Yes	30 (56.6%)
No	23 (43.4%)
Previous systemic therapy, n (%)	
None	47 (88.7%)
Immunotherapy	3 (5.7%)
Target therapy	3 (5.7%)
Number of metastatic sites, n (%)	
1	9 (17.0%)
2	20 (37.7%)
>2	24 (45.3%)
Sites of metastases, n (%)	
Lung	40 (75.5%)
Lymph nodes	25 (47.2%)
Bone	21 (39.6%)
Liver	15 (28.3%)
Brain	4 (7.5%)
Other	22 (41.5%)

KPS: Karnofsky performance status.

Treatment patterns

Table-2 summarizes the sunitinib treatment patterns and reasons for discontinuation. Thirty seven patients (69.8%) started on therapy at the standard schedule of 50mg once daily, 4 weeks on, followed by 2 weeks off; sixteen patients (30.2%) started treatment at a reduced dose. Although not statistically significant, patients on standard regimen were younger (median age: 58.6 versus 68.8 years; p=0.1) than those on reduced dose regimens. Median TTD was 3.30 months (95% CI: 1.96-4.63). At the time of analysis, almost all patients had discontinued therapy (96.2%), mostly due to disease progression (69.8%). Drug toxicity caused treatment interruption in 26.4% of patients. Furthermore, adverse events required dose modifications in 26.4% of patients. Three patients (5.7%) experienced dose escalation after starting treatment at a reduced dose.

Safety

Adverse events reported in patients' medical charts are summarized in Table-3. Among patients included in this retrospective analysis, 94.3% experienced at least one AE, including grade 3 or higher AE. The most common all-grade AE was fatigue or asthenia (64.1%), followed by nausea (49.0%), stomatitis (41.5%), vomiting (37.7%) and hypothyroidism (32.1%). Grade 3 or higher AE was reported in 39.6% of patients. The most common grade 3 or higher AE were fatigue (15.1%), neutropenia (9.5%), nausea, vomiting, and diarrhea (7.5% each). There was one treatment-related death due to febrile neutropenia and septic shock. There was no statistically significant difference in the frequency of grade 3 or higher AEs between patients who started sunitinib at the standard dose and patients who initiated therapy at a reduced dose regimen.

Table 2 - Sunitinib treatment patters.

	Number of patients (n = 53)
Initial dose	
- 50mg QD 4weeks on 2 off	37 (69.8%)
- Reduced dose	16 (30.2%)
Duration of treatment, months	
- Median (95% CI)	3.30 (1.96 – 4.63)
Patients with sunitinib dose reduction	14 (26.4%)
Status of sunitinib treatment at time of analysis	
- Discontinuation due to disease progression	37 (69.8%)
- Discontinuation due to adverse events	14 (26.4%)
- On treatment	2 (3.8%)

CI: confidence interval; **QD:** once daily.

Table 3 - Reported adverse events during sunitinib treatment*.

Adverse event	All grades, n (%)	Grades 3/4, n (%)
Any	50 (94.3)	21 (39.6)
Fatigue/asthenia	34 (64.1)	8 (15.1)
Nausea	26 (49.0)	4 (7.5)
Stomatitis	22 (41.5)	3 (5.7)
Vomiting	20 (37.7)	4 (7.5)
Hypothyroidism	17 (32.1)	2 (3.8)
Anemia	12 (22.6)	1 (1.9)
Hand-foot syndrome	12 (22.6)	3 (5.7)
Hypertension	10 (18.8)	-
Diarrhea	9 (16.8)	4 (7.5)
Neutropenia	7 (13.3)	5+ (9.5)
Thrombocytopenia	7 (13.3)	2 (3.8)

*Adverse events experienced by at least 10% of patients are reported; +Including a grade 5 adverse event.

Efficacy

Of the 53 patients included in this analysis, nine (17.0%) achieved partial response, 12 (22.6%) had stable disease and 13 (24.5%) had progressive disease. Nineteen patients (35.8%) were not evaluated for response, including 14 patients (26.4%) with early discontinuation: one treatment-related death caused by febrile neutropenia; one loss to follow-up before response evaluation; and 4 (7.5%) cases of early discontinuation due to limiting AE. No complete responses were seen. At a median follow-up of 7.5 months, 9 patients

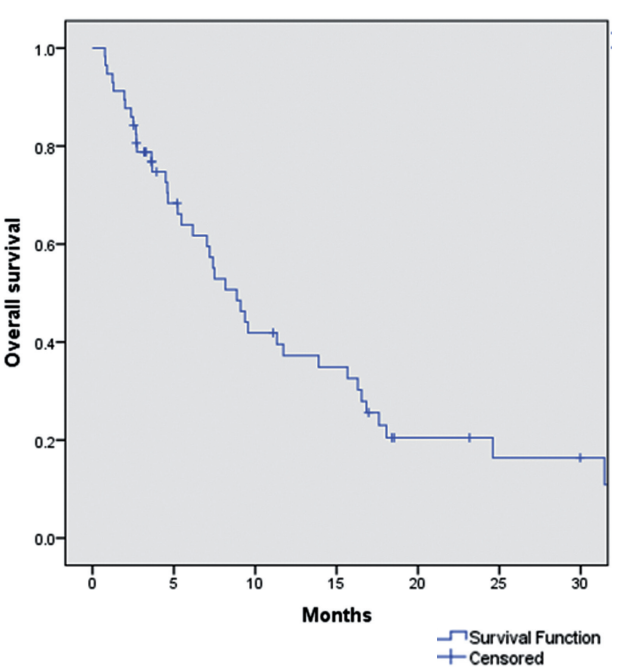
(16.9%) were still alive. The estimated median OS was 8.16 months (95% CI, 5.73-10.59) (Figure-1). There was no statistically significant difference in median OS between patients who started sunitinib at the standard dose (9.1 months; 95% CI, 6.12-12.07) and patients with modified regimens (7.2 months; 95% CI, 6.28-8.11). Only 6 patients received a subsequent treatment after discontinuing sunitinib (five of them were treated with interferon-alpha and one was treated with everolimus).

DISCUSSION

Data regarding the use of sunitinib in patients with poor-risk mRCC are scarce and therefore, data on efficacy and safety of this therapy in this population are less known. Although patients experienced an OS of 8.16 months in this analysis, a high proportion of grade 3 or higher AEs occurred (39.6%) and 26.4% of patients discontinued treatment due to toxicity, regardless of starting treatment at a reduced dose.

Here, we describe a median OS of 8.16 months (95% CI, 5.73-10.59), with only 11.3% of patients exposed to second line therapy, which highlights a potential survival benefit of sunitinib in the setting of poor-risk patients. This finding is consistent with the results from both the IDC original and external validation datasets demonstrated that poor-risk patients show a median OS of 8.8 and 7.8 months, respectively (4, 7) and compares favorably to subset analysis of phase III and IV trials (8, 9). In the pivotal phase III trial only 6.4% patients with poor-risk MSKCC criteria were included, rendering a median OS of 5.3 months (95% CI: 4.2–10.0 months) with sunitinib compared with 4.0 months (95% CI: 2.7–7.2 months) with IFN-alpha (HR: 0.660; 95% CI: 0.360–1.207) (8). Similarly, the expanded access program (EAP) included 9% poor-risk patients according MSKCC criteria (373 out of 4564 total subjects) and found the same median OS of 5.3 months (95% CI: 4.6–5.4 months) (9). It must be highlighted that the numerical variations in median OS described across these different studies might be, at least in part, due to the fact of different poor risk classification, since 14% of MSKCC intermediate-risk patients are reclassified as poor-risk when stratified by IDC criteria (4).

Figure 1 - Kaplan-Meier estimates of overall survival was 8.16 months (95% confidence interval, 5.73-10.59).



In our series, an ORR of 17.0% was achieved and 22.6% of the evaluable patients achieved stable disease. No literature data on response rate restricted to poor risk patients is available; however, in EAP trial, which included different risk subgroups, an ORR of 17%, was reported (9). Considering that 26.4% of our population died before response assessment, it is possible that the rate of patients who truly benefit from sunitinib is really lower. However, the lack of a predefined interval for response assessment in our retrospective series could also justify, at least in part, the lower ORR of single-agent reported here.

Other main issues addressed by our study were safety and treatment patterns. Although grade 1 and 2 AE might have been underreported, a high proportion (39.6%) of patients experienced grade 3 or higher AEs. In our series, the rates of grade ≥3 fatigue, nausea, vomiting, and diarrhea are higher than those previously reported in both controlled and non-controlled studies (Table-4) (8-12). The high proportion of serious AE might be explained by the broader eligibility criteria. Some of the included patients had poor KPS

Table 4 - Reported grade 3 or higher adverse events in studies evaluating sunitinib in mRCC population.

Study	Type of study	Any event	Fatigue	Diarrhea	Vomiting	Nausea
Barroso-Sousa, et al.*	Retrospective	39.6%	15.1%	7.5%	7.5%	7.5%
Motzer, et al.[8]	Phase III	NR	11.0%	9.0%	4.0%	5.0%
Gore, et al.[10]	Phase IV	NR	8.0%	5.0%	3.0%	2.0%
Chouery, et al.[11]	Retrospective	NR	11.0%	7.0%	2%	0%
Porta C, et al.[12]	Retrospective	27.1%	9.4%	0%	5.9%	3.5%
Feinberg, et al.[13]	Retrospective	29.8%	5.3%	2.3%	0.8%	1.5%

mRCC: metastatic renal cell carcinoma; *current paper

(60-70), which are commonly treated under routine care, albeit excluded from randomized clinical trials (13). Furthermore, our analysis showed that 26.4% of patients discontinued sunitinib due to AE, which is higher than rates of 8-20% in other studies (9, 10, 14). In this study, 30.2% of our patients started at the standard dose of standard dose of sunitinib. This finding might reflect the concern of AE on patients with poor KPS and older age treated with sunitinib. A recent analysis showed that approximately 30% of elderly patients treated with sunitinib start therapy with reduced dose (15). However, in our analysis there were no were statistically significant difference in rates AE between these two groups of patients.

Although previous studies have examined activity and safety of sunitinib outside a clinical trial, to our knowledge, this is the first observational study that specifically addressed the efficacy, safety and treatment patterns of this treatment in a poor-risk population according IDC model. Furthermore, our data reflect a "real-world" practice setting, and OS could be accurately estimated and was consistent with that reported in the literature.

CONCLUSIONS

Our study confirms that sunitinib can be a feasible and active treatment for some patients with mRCC and poor risk features. However, the high incidence of AE and the drug discontinuation rates suggest a need for careful monitoring. Considering the incurable nature of advanced RCC, this retrospective study indicates that continued research efforts to identify more effective and better tolerated treatments for mRCC are needed, especially for poor risk patients.

ACKNOWLEDGMENTS

This work received no specific grant from any funding agency in the public, commercial, or nonprofit sectors.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 40 (6): 842-845, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.17

New head-mounted display system applied to endoscopic management of upper urinary tract carcinomas

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ABSTRACT

Purpose: We tested a new head-mounted display (HMD) system for surgery on the upper urinary tract.
Surgical Technique: Four women and one man with abnormal findings in the renal pelvis on computed tomography and magnetic resonance imaging underwent surgery using this new system. A high definition HMD (Sony, Tokyo, Japan) is connected to a flexible ureteroscope (Olympus, Tokyo, Japan) and the images from the ureteroscope are delivered simultaneously to various participants wearing HMDs. Furthermore, various information in addition to that available through the endoscope, such as the narrow band image, the fluoroscope, input from a video camera mounted on the lead surgeon's HMD and the vital monitors can be viewed on each HMD.
Results: Median operative duration and anesthesia time were 53 and 111 minutes, respectively. The ureteroscopic procedures were successfully performed in all cases. There were no notable negative outcomes or incidents (Clavien-Dindo grade ≥1).
Conclusion: The HMD system offers simultaneous, high-quality magnified imagery in front of the eyes, regardless of head position, to those participating in the endoscopic procedures. This affordable display system also provides various forms of information related to examinations and operations while allowing direct vision and navigated vision.

ARTICLE INFO

Key words:
Urinary Tract; Ureteroscopy; Natural Orifice Endoscopic Surgery; Video-Assisted Surgery

Int Braz J Urol. 2014; 40: 842-5

Submitted for publication:
January 21, 2014

Accepted after revision:
April 06, 2014

INTRODUCTION

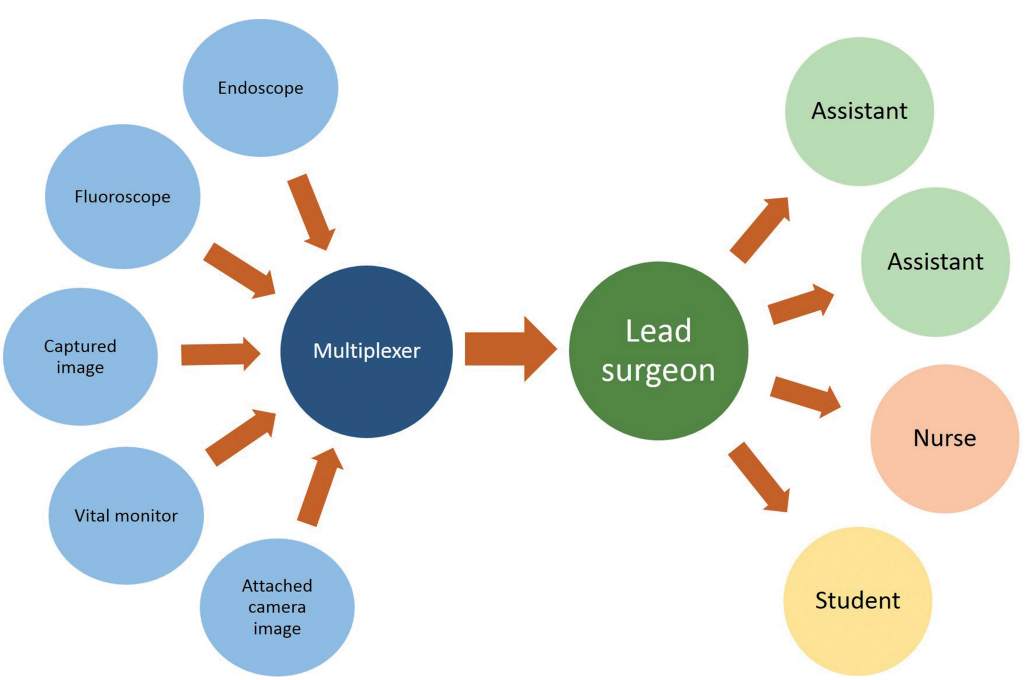
With the development of excellent smaller and flexible ureteroscopes, the ureteroscopic management of the upper urinary tract (UUT) and upper urinary tract urothelial carcinomas (UUTUC) has become more practical, and indications for such procedures have expanded from those patients with solitary kidney or renal insufficiency to patients with normal contralateral kidney (1). In order to make ureteroscopy more feasible and effective, we applied a novel head-mounted display (HMD) system that displays simultaneous, high-quality magnified imagery in front of the eyes, regardless of head position, to those participating in endoscopic procedures. This affordable display system also provides various forms of information related to examinations and operations while allows direct vision and navigated vision. In this study, we describe an application of the system in UUT examinations.

SURGICAL TECHNIQUE

Four women and one man with abnormal findings in the renal pelvis on computed tomography (CT) and magnetic resonance imaging (MRI) underwent surgery using this new system. Each patient had irregular images in the renal pelvis on CT and low T2-weighted signals and diffuse high-intensity signals on diffusion-weighted MRI imaging, leading to suspicion of urothelial carcinoma of the renal pelvis. For further evaluation, ureteroscopy and, if possible, biopsy of the abnormal urothelium tissue with reference to the narrow band image (NBI) was performed. The patients gave written informed consent to participate in a clinical trial to the institutional investigational review board of our institution.

The system presented here is used as follows (Figure-1). A high definition HMD (Sony, Tokyo, Japan) is connected to a flexible ureteroscope (Olympus, Tokyo, Japan) and the images from the ureteroscope are delivered simultaneously to various participants wearing HMDs. This monitor is fitted with 0.7-inch (18.0mm diagonal) Organic Light-Emitting Diode panels with displayed pixel count of 1280x720. The device is already commercially available in Japan and Europe. Its purchase costs are €12300. Furthermore, the devices have four different input-output terminals, including Digital Video Interface and Serial Digital Interface. Various informations in addition to that available through the endoscope, such as the NBI, the fluoroscope, input from a video camera mounted on the HMD and the vital monitors can be viewed on each head-mounted display (Figure-2A). Technical support was provided by the Sony Corporation. Two urologists (one lead surgeon and one assistant) performed the operation. Both the lead surgeon and the assistant each wore an HMD throughout the procedure. The imaging information obtained from the ureteroscope, captured narrow band image (NBI), images from the video camera attached to the HMD of the lead surgeon, and the patient's vital signs monitor are split using an imaging splitter (400-VGA003, Sanwa Supply Incorporated, Okayama, Japan) and the composite image is outputted into two multiplexers (VPM-H1, MEDIAEDGE Corporation, Hyogo, Japan).

Figure 1 - A schematic view of the head-mounted display (HMD) and personally integrated monitoring system. Multiple input information is split using an imaging splitter and integrated into one composite image using a multiplexer. Each wearer of an HMD can independently arrange the array of the displayed images.



The images are integrated using a four-split screen technique on the multiplexer and are displayed on the HMDs (Figure-2B). The lead surgeon usually opts to arrange the ureteroscopic view as the main image displayed by the HMD during the observation and biopsy, and the assistant may choose the fluoroscopic view as the main image.

Median operative duration and anesthesia time were 53 and 111 minutes, respectively. The ureteroscopic procedure was successfully performed in all cases. Tumor biopsy was performed with a 3F cup biopsy forceps for flat or sessile lesions. There were no notable negative outcomes or incidents in the postoperative courses (Clavien--Dindo grade ≥1) of any patients (Table-1). During the procedures, neither the lead surgeon nor the assistant surgeon experienced any HMD-related adverse effects no reported any discomfort. Of all the patients, 3 patients were diagnosed as having urothelial carcinoma and subsequently treated with radical nephroureterectomy.

COMMENTS

This is the first study to use the HMD system in ureteroscopy and we safely completed the procedures in a reasonable time by using the features of HMD system. There were no intra-operative or postoperative complications.

Traditionally, nephroureterectomy has been the treatment of choice for UUTUC. As population of the elderly increases, the number of

Figure 2 - Photograph of ureteroscopy being performed using the head-mounted display (HMD) system. Both the lead surgeon and the assistant wear an HMD during all stages of the procedure (A). Captured images of the integrated image data include an ureteroscopic image, a fluoroscopic image, the patient's vital signs, and the view from a camera attached to the HMD worn by the lead surgeon (B).

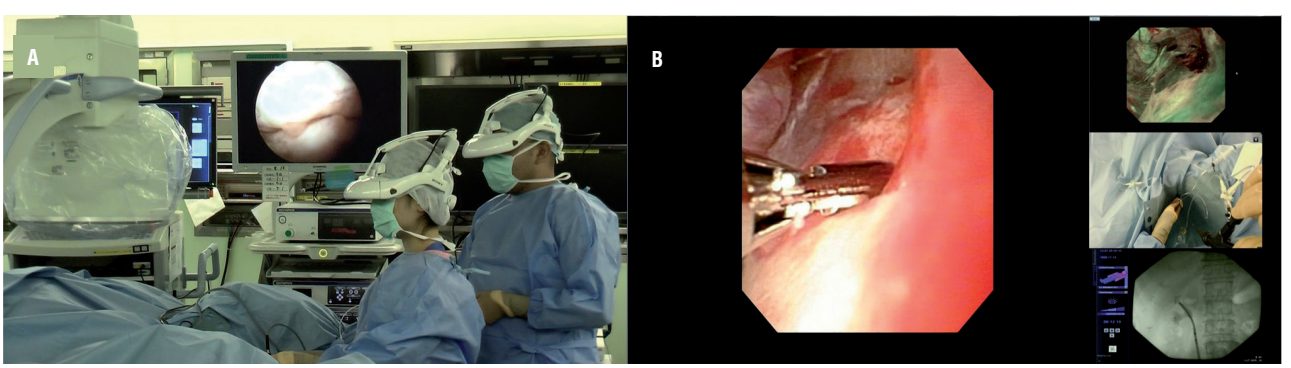


Table 1 – Patients' clinical data and outcomes.

Age	Gender	Lesion	ASA score (min.)	Operative duration (min.)	Duration of anesthesia	Clavien-Dindo grade ≥ 1	Pathological diagnosis	Subsequent treatment
62	Female	Right RP	2	73	139	none	UC, G2	NU
45	Female	Left RP	1	19	43	none	no malignancy	observation
69	Female	Right RP	1	62	136	none	no malignancy	observation
79	Female	Right RP	1	50	120	none	UC, G2	NU
76	Male	Right RP	2	63	117	none	UC, G1	NU

RP = Renal Pelvis; **ASA =** American Society of Anesthesiologists; **UC =** urothelial carcinoma; **NU =** nephroureterectomy

patients with a decreased estimated glomerular filtration rate (ill compromised contralateral kidney, solitary kidney) increase, and the importance of endoscopic management is also increasing (1). Furthermore, the indications for endoscopic management have expanded to include those patients without significant renal parenchymal disease or comorbidities, and specifically those with a normal contralateral kidney as well as imperative cases (2).

Although retrograde endoscopic procedures have become more practical and efficacious with the development of new endoscopic tools, ureteroscopy is still troublesome because the procedure usually requires a variety of information from different screens. To offer better endoscopic management of UUT, we have tested a new HMD system, which we had already applied to minimally invasive endoscopic surgery (3). The HMD system has five visual functions: magnified vision, panoramic vision, multiple vision, shared vision, and navigated vision. The magnified view of the endoscopic image can be displayed in front of the user's eyes. We have not experienced serious malfunction events during the procedure because the HMD also allows direct vision without the need to remove the headset. When the user looks downward, direct unimpeded vision is possible. Multiple and shared vision can be provided by using a signal changer. The HMD can display multiple informations from several imaging sources, and this can also be delivered to many participants simultaneously (4). Navigation with composite images, such as fluoroscopic images and NBI images, make it easier for surgeons to perform various procedures.

The present study has several limitations, including the small sample, the lack of control group and the lack of cost analysis. There is still a lot to be done in order to demonstrate the actual advantages in terms of oncological outcomes and cost-effectiveness. We think that much larger cohorts and longer follow-up would be needed.

In conclusion, the HMD system can be safely applied to ureteroscopy. The HMD system offers simultaneous, high-quality magnified imagery in front of the eyes, regardless of head position, to those participating in endoscopic procedures. This affordable display system also provides various forms of information related to examinations and operations while allowing direct vision and navigated vision.

CONFLICT OF INTEREST

Dr. Kihara has received research funding from Sony Corporation (Tokyo, Japan), but the sponsor had no control over the interpretation, writing, or publication of this work.

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Vol. 40 (6): 846-852, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.18

Continuous renal replacement therapy in children with multiple organ dysfunction syndrome: A case series

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ABSTRACT

There is a lack of definitive information regarding the precise indications, implementation, and outcomes of continuous renal replacement therapy (CRRT) for the treatment of critically ill children. Six children (three boys, three girls) aged from 3 days to 8 years, all of whom had multiple organ failure, were submitted to bedside CRRT using M60 filter membranes. Modified Port carbonate formula was used and clotting time was maintained between 20 and 30 minutes. Activated partial thromboplastin time was 1.5- to 2-fold normal. One patient discontinued treatment due to family decision. Marked improvements were seen in the remaining five patients, including normalization of blood urea nitrogen and creatinine levels, stabilization of electrolytes, and improvements in markers of organ function. Of note, one patient (a six-year-old male) underwent the treatment for 241 hours. All five patients were subsequently discharged and recovered uneventfully. CRRT is effective for the management of children who are critically ill due to multiple organ failure.

ARTICLE INFO

Key words:
Child; Organ Dysfunction Scores; Renal Replacement Therapy; Multiple Organ Failure

Int Braz J Urol. 2014; 40: 846-52

Submitted for publication:
November 05, 2013

Accepted after revision:
April 06, 2014

INTRODUCTION

Continuous renal replacement therapy (CRRT) is frequently used for the treatment of critically ill children with acute kidney disease (1). Although such treatment can be effective (2,3), there is still a lack of consensus concerning the precise indications, the implementation, and the associated outcomes regarding CRRT in children (2,4). Therefore, we felt compelled to share our experience using this approach for treating critically ill children. Specifically, we describe the treatment and outcomes for a series of six critically ill children, all of whom had multiple organ dysfunction syndrome (MODS).

MATERIALS AND METHODS

Patients

All children were treated in the pediatric intensive care unit of the First Affiliated Hospital of Xiamen University between February 2008 and June 2011. There were three boys and three girls (Tables 1 and 2 for demographic and clinical

Table 1 - Demographic and treatment characteristics of critically ill children with multiple organ dysfunction syndrome who received continuous renal replacement therapy.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, years	6	7	1.5	3 days	4	8
Gender	Male	Female	Male	Female	Female	Male
Weight, kg	23	13	11	4	10	23
Vascular access	RFV	RFV	RFV	RSCV	RFV	RFV
Catheter	8.5Fr	8.5Fr	6.5Fr	6.5Fr	6.5Fr	8.5Fr
Dialysis filter	M60	M60	M60	M60	M60	M60
Anticoagulant	Heparin	Heparin	No heparin	Heparin	No heparin	Fragmin
First dose, units	500	NA	NA	100	NA	1000
Maintenance dose (units/h)	104-331	62.5	NA	62.5-125	NA	500 (4 h)
Treatment modality	CVVHDF	CVVHDF	CVVHDF	CVVH	CVVH	CVVHDF
Blood flow rate, mL/min	80	75	30	30	60	60
Replacement fluid flow rate, mL/h	600	1000	300	500	800	400
Dialysate flow rate, mL/h	300	500	200	0	0	300
Fluid removal rate, mL/h	50-100	0-50	0-40	20-60	0	0
Duration of CRRT, h	241	86	12	52	5	6

CRRT: continuous renal replacement therapy; **CVVHDF:** continuous venovenous hemofiltration with dialysis; **CVVH:** continuous venovenous hemofiltration; **NA:** not available; **RFV:** right femoral vein; **RSCV:** right subclavian vein.

characteristics). All suffered from MODS (Table-3) due to sepsis and acute rhabdomyolysis syndrome (Case 1), septic shock (Cases 2, 3, and 6), neonatal asphyxia and meconium aspiration syndrome (Case 4), or hemorrhagic shock, ureter and bladder rupture, and crush syndrome (caused by a car accident) (Case 5).

Treatment

A PRISMA bedside CRRT machine (Hospal, Lyon, France) and M60 AN69 membrane filters were used for all patients. Double- or single-lumen veno-venous hemodialysis catheters were inserted via the right femoral or subclavian vein. The replacement fluid (modified Port carbonate formula) was infused using the post--dilution method. For anticoagulation, patients received heparin or low molecular weight heparin (note: some patients did not receive heparin). Clotting time was maintained between 20 and 30 minutes and tested using the capillary tube method. Activated partial thromboplastin time was 1.5-2.0 times normal.

Outcomes

One patient (case 5) discontinued treatment due to a family decision and eventually died due to circulatory failure and electrolyte disturbance. Dramatic improvements were seen in clinical measures after treatment in all other patients (Table-2). Of note, blood urea nitrogen (BUN) and creatinine (Cr) levels were normalized, electrolyte and acid-base balance was stabilized, and indicators of organ function were markedly improved. These patients were subsequently discharged.

Below, we describe two cases of particular interest in more detail.

Table 2 - Clinical characteristics of critically ill children with multiple organ dysfunction syndrome before and after continuous renal replacement therapy.

Characteristic	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Body temp, ºC	39.3	36.8	37.7	36.5	37.7	36.5	36.5	37	38.2	35.5	39.1	36.4
BP, mmHg	70/48	96/50	85/45	104/74	81/52	102/68	NA	NA	55/32	84/30	65/35	108/73
Urine output, mL	140	1740	30	915	NA	NA	170	1600	0	800	1280	1620
WBC, $\times 10^9$/L	26.9	8.4	23.03	6.5	12.1	2.2	20.2	8.6	12.41	7.25	21.98	9.8
Hb, g/L	94	143	83	96	156	103	149	139	88	59	144	78
Platelets, $\times 10^9$/L	197	354	49	162	411	436	150	144	160	210	250	243
BUN, mg/dL	43.820	28.089	95.084	54.214	60.393	54.491	NA	NA	NA	NA	16.9	1.5
Creatinine, mg/dL	4.28	0.86	3.51	0.94	3.48	1.88	2.31	1.75	2.17	1.76	1.36	0.27
ALT, U/L	10382	173	116	31	72	NA	577	141	173	NA	82	71
AST, U/L	13891	140	615	20	51	NA	686	41	511	NA	315	280
TBIL, mg/dL	0.4678	0.234	1.053	0.351	0.175	NA	1.286	0.8198	0.234	NA	15	5
DBIL, mg/dL	0.117	0	0.468	0.117	0	NA	0.526	0.234	NA	NA	7	3
Albumin, g/L	25	36	17	28	43	NA	30	32.4	NA	NA	24	30
Creatine kinase, U/L	23057	24	374	299	30	NA	NA	195	8000	NA	13586	126
CRP, mg/L	>90	11	>90	0.51	26	NA	8	NA	NA	NA	18	5
K^+, mg/dL	13.294	19.159	16.031	17.595	23.851	13.294	19.941	13.490	28.543	19.941	9.384	16.813
Ca^{2+}, mg/dL	7.9358	9.860	6.894	8.617	3.888	4.730	4.930	9.619	6.092	5.170	7.375	7.174
Na^+, md/dL	280.487	321.86	305.767	340.252	308.066	303.468	278.179	289.674	301.169	308.066	344.85	312.664
Cl^-, mg/dL	333.23	350.955	258.045	354.5	350.955	326.14	304.87	290.69	365.135	354.5	340.32	361.59
APTT, s	63.6	39.2	84.8	13.9	12.8	23	33.9	29.1	NA	179.3	143.9	34.1
PT, s	28.6	12.7	45.5	36.6	35.7	39	15.8	15.3	NA	34.1	18.9	14.2
INR	5.82	0.97	5.03	1.09	4.31	1.07	1.11	1.17	3.61	NA	1.62	1.12
CO_2-CP, Vol%	23.596	48.972	44.52	57.876	26.712	53.424	30.051	65.222	NA	NA	19.7	24.1

ALT: alanine transaminase; **APPT:** activated partial thromboplastin time; **AST:** aspartate transaminase; **BP:** blood pressure; **BUN:** blood urea nitrogen; **CRP:** C-reactive protein; **DBIL:** direct bilirubin level; **Hb:** hemoglobin; **INR:** international normalized ratio; **NA:** not available; **PT:** prothrombin time; **TBIL**: total bilirubin level; **WBC:** white blood cell count.

Table 3 - Summary of multiple organ dysfunction scores for each critally ill child who received continuous renal replacement therapy.

Case	Respiration	Kidney	Liver	Blood System	Nervous System	Total
1	2	2	1	1	2	8
2	2	2	2	3	2	11
3	2	2	1	2	2	9
4	2	2	2	2	2	10
5	2	2	2	1	2	9
6	2	2	1	1	2	8

Case 1

Case 1 was a six-year-old boy who was admitted on 9 January 2011 with a two-day history of non-projectile vomiting and diarrhea, yellow watery stool, and fever. He had also experienced a convulsion. After admission, the patient was diagnosed with toxic bacterial enteritis, sepsis, MODS (acute kidney injury [AKI], stress ulcer, infection-induced toxic encephalopathy, early disseminated intravascular coagulation, acute myocardial injury, acute liver injury, acute rhabdomyolysis), hyponatremia, metabolic acidosis, and hypoalbuminemia. The patient was experiencing blurred consciousness on admission and suffered a convulsion the day after admission, with a concomitant sustained decrease in blood pressure and urine output. Blood testing revealed abnormal coagulation, metabolic acidosis, electrolyte imbalance, and progressively increased BUN and Cr levels. Serum Cr peaked at 378μmol/L, while creatine kinase was 23057 U/L. The patient underwent CRRT from 11-20 January, and regained consciousness on January 16th. His liver and renal function gradually improved, and blood pressure and urine output normalized. The patient underwent CRRT for 241 hours and was hospitalized for 33 days before discharge. After discharge, the patient was followed-up once-monthly for six months. His development was normal and there was no relapse of symptoms/biochemical abnormalities.

Case 4

Case 4 was a three-day-old female neonate who was transferred to the neonatal intensive care unit on 16 February 2008. She had a history of no crying, poor responsiveness, and anuria. Diagnoses after admission were neonatal asphyxia and meconium aspiration syndrome, neonatal AKI, MODS (heart, liver, kidney, brain), neonatal hypoxic encephalopathy, and severe electrolyte imbalance. Her serum Cr was 204μmol/L on admission and 429μmol/L on the day after admission. CRRT was initiated. Her electrolytes and urine output gradually normalized. The patient underwent bedside CRRT for 52 hours and was hospitalized for 20 days before discharge. After discharge, the patient was followed-up once--monthly for six months. Her development was normal and there was no relapse of symptoms or biochemical abnormalities.

DISCUSSION

Herein, we have summarized our experience treating six children with MODS using CRRT. Of the five children who received full treatment, all recovered completely, thus supporting the effectiveness of CRRT for the management of children who are critically ill due to MODS.

Two cases in our series warrant further discussion, Cases 1 and 4. Case 1 was a six-year--old boy, whereas Case 4 was a three-day-old female neonate; both were in critical condition and would have died without intervention. Case 1 was unique for the duration of CRRT (241 hours), whereas Case 4 was unique because there have been few reports of survival in neonates with MODS af-

ter CRRT (3,5,6). In both of these cases, and indeed in general, we believe that early intervention with CRRT may have inhibited the cytokine cascade/systematic inflammatory response and the associated inflammatory injury (7). Clearly, the amelioration of uremia and fluid overload likely contributed to the efficacy of treatment. According to our review of the literature, CRRT for 241 hours is very rare. This duration of treatment was necessary to stabilize the patient's internal environment, provide nutritional/metabolic support, and allow for the implementation of other supportive treatment. For this patient, an AN69 membrane filter M60 with good biocompatibility, high permeability, and a strong adsorption capacity was used. The area of the filter was relatively large (0.6m^2). The membrane, which can also be used under hypotension, causes a weak activation of complement and leukocytes, and has a small impact on hemodynamics. The high-permeability of this membrane may help to improve the anti-inflammatory cytokine to proinflammatory cytokine ratio, down-regulate the body's inflammatory response, and ameliorate the systemic inflammatory response (8).

One of the keys to early intervention in the neonate was placement of a central venous catheter by an experienced anesthesiologist. The smallest M60 filter was used and the tubing was pre-filled with whole blood. Further, at the beginning of CRRT, the blood flow rate was low, thus preventing a subsequent drop in blood pressure (9). Attention was also paid to body heat preservation and heating the vascular access point. This case highlights that, in addition to having the appropriate equipment, inter-departmental cooperation can be important for successful CRRT. Staff in neonatal/pediatric intensive care units should not hesitate to seek assistance from staff in other departments who may have appropriate expertise in central vein cannulation and CRRT.

We also believe it is worthwhile to summarize the key technical principles and requirements for successful implementation of CRRT in children. Due to the physiological and anatomical characteristics of children, including low body weight, small blood flow volume, and hemodynamic instability, filters and tubing with a low pre-filled volume should be used to reduce the blood volume in extracorporeal circulation and help ameliorate the decrease in effective circulating blood volume. Filters with a high molecular weight polymer membrane, high permeability, good biocompatibility, and a small impact on the coagulation system should be selected. The use of AN69 membranes has been linked to bradykinin release syndrome among patients who are acidotic or taking angiotensin converting enzyme inhibitors (10,11). Alternative membranes should be used in such cases. Generally, the blood volume in extracorporeal circulation should be maintained at <10% of body weight, ie, <30mL in neonates, <50mL in infants, and <100mL in children. For neonates weighing <2.5kg, tubing can be pre-filled with plasma, whole blood, or 5% albumin (12).

Establishing vascular access is a key factor for successful CRRT in children. The most frequently used veins in children are the femoral and internal jugular. For operative easiness and to help maintain stable blood flow, veno-venous double-lumen hemodialysis catheters are often used. Two single-lumen venous hemodialysis catheters can be used in infants. Recommended catheters by age are: <6 months, 4-5F single-lumen; 6-12 months, 5-7F double-lumen; 1-3 years, 8-9F double-lumen; and >3 years, 8-12F double-lumen (13).

Determining the therapeutic dose for continuous veno-venous hemofiltration in critically ill children remains a challenge. Individual doses should be determined according to the disease conditions, taking into consideration metabolic state, fluid volume, and duration of dialysis (14). Transmembrane pressure should be monitored and maintained at <200mmHg (note: a transmembrane pressure >250mmHg may indicate clotting in the filter) (15). Particular attention should be paid to warming the replacement fluid. The recommended flow rates are as follows. Blood flow: 30mL/min in neonates; 30-40mL/min in infants/young children; 50-75mL/min in children weighing <20kg; and 75-100mL/min in children weighing >20kg. Ultrafiltration rate: 8-10mL/min/m^2 in neonates/infants; 8-15mL/min/m^2 in children (note: daily fluid input/output, cardiac function, and edema should be considered). Dialysates: 15-20mL/min/m^2 in neonates/infants/children (16).

We believe there are a number of key factors that should be taken into account when considering CRRT in cases similar to those described herein. For cases involving AKI or acute renal failure, particular attention should be paid to water and sodium retention and blood nitrogen levels, all of which have a significant impact on the treatment and survival of infants and young children (17), as well as the speed of progress. The characteristics of systemic disease are also an important factor (18). CRRT rescue was successful in the 5 patients described herein who completed treatment. We believe that several reasons underlie this high rate of treatment success. First, the decision to treat with CRRT was made early. Our approach is consistent with that advocated by Wolf et al., who suggest that the survival rate following extracorporeal circulation can be improved if treatment is commenced as soon as possible (19). Second, CRRT allows for correction of water and sodium retention and electrolyte imbalances in a timely manner, facilitating the effectiveness of other treatments (20). Finally, we must reiterate, that involvement and cooperation between a multi-disciplinary team is of paramount importance so that appropriate rescue of respiratory failure, use of breathing machines, infection prevention and treatment, and cardiovascular support can be accomplished. With regards to when to withdraw treatment, we believe that CCRT can be halted once water and sodium retention subsides, urine output returns to normal, and renal function recovers. To this end, it is worth noting that body water load and urine output are directly related to survival in children (4, 21).

Over the last few decades, CRRT has become increasingly used in pediatrics, particularly for treating critical illness, such as severe acute renal failure and MODS (9). With further study into the mechanisms underlying the efficacy of CRRT and technological advances, the effectiveness of CRRT for treating critically ill children can only improve. We hope the sharing of our experience with this treatment will help facilitate such improvement.

ABBREVIATIONS

AKI = acute kidney injury
ALT = alanine transaminase
APPT = activated partial thromboplastin time
AST = aspartate transaminase
BP = blood pressure
BUN = blood urea nitrogen
Cr = creatinine
CRP = C-reactive protein
CRRT = continuous renal replacement therapy
CVVHDF = continuous venovenous hemofiltration with dialysis
CVVH = continuous venovenous hemofiltration
DBIL = direct bilirubin level
Hb = hemoglobin
INR = international normalized ratio
MODS = multiple organ dysfunction syndrome
NA = not available
PT = prothrombin time
RFV = right femoral vein
RSCV = right subclavian vein
TBIL = total bilirubin level
WBC = white blood cell count

CONFLICT OF INTEREST

None declared.

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CHALLENGING CLINICAL CASES

Vol. 40 (6): 853-857, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.19

Extra corporeal shockwave lithotripsy resulting in skin burns – a report of two cases

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ABSTRACT

Severe skin injury after extracorporeal shock wave lithotripsy (ESWL) is rare. We describe two patients who suffered full thickness skin burns following ESWL for renal calculi. One patient was treated conservatively and the other underwent debridement with skin grafting. We speculate that failure of the thermostatic mechanism of the lithotripter, leading to overheating of the water-filled cushion, resulted in this very rare adverse event. Proper preoperative patient counseling regarding the risk of serious burn injuries will help to avoid potential litigation.

ARTICLE INFO

Key words:
skin, burn, lithotripsy, complication

Int Braz J Urol. 2014; 40: 853-7

Submitted for publication:
December 17, 2013

Accepted after revision:
March 16, 2014

INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL) is well established as a safe and efficacious mode of treatment of renal and upper ureteric calculi. Despite the low morbidity, a few rare serious adverse events have been reported in the literature. We report an unusual complication in two patients following ESWL which resulted in full thickness skin burns to the flank.

CASE REPORT

Case 1 - The patient was a 59 year old female with a 5mm right lower calyceal calculus and recurrent UTI. She had a history of nephrolithiasis for which she had undergone multiple interventions in the past including ureteroscopy with laser lithotripsy and ESWL. She had multiple co-morbidities including poorly controlled type II diabetes, pulmonary hypertension, hypothyroidism, breast malignancy, osteoarthritis, GERD, obesity, atrial fibrillation. Medications included metformin, insulin, diltiazem, hydralazine, lisinopril, Synthroid®, metoprolol and sotalol.

The lithotripter used was the LithoTron® (Healthtronics, Atlanta, GA). The coupling medium used was the Sonotech Clear Image® ultrasound gel, a high viscosity gel containing no bubbles. General anesthesia was induced and the

patient was positioned appropriately over the lithotripter. With the stone adequately localized under fluoroscopy in the right lower calyx, 3,000 shocks were delivered at a rate of 120 shocks per minute at a power of 24 kV. The lithotripter was operated by an experienced lithotripsy technician and the urologist was present in the room throughout the entire procedure.

Immediately after the procedure, following removal of the shock-head, the patient was found to have minor erythematous skin changes with petechiae over the area shocked. She then developed blisters and worsening pain and was admitted overnight for observation. She was discharged home the following day with instructions for daily dressings. She was seen in clinic four days later with bullous lesions and a 10 x 12cm superficial burn of the right flank. KUB showed stone clearance and the patient was discharged with instructions for Mepilex® dressing every other day.

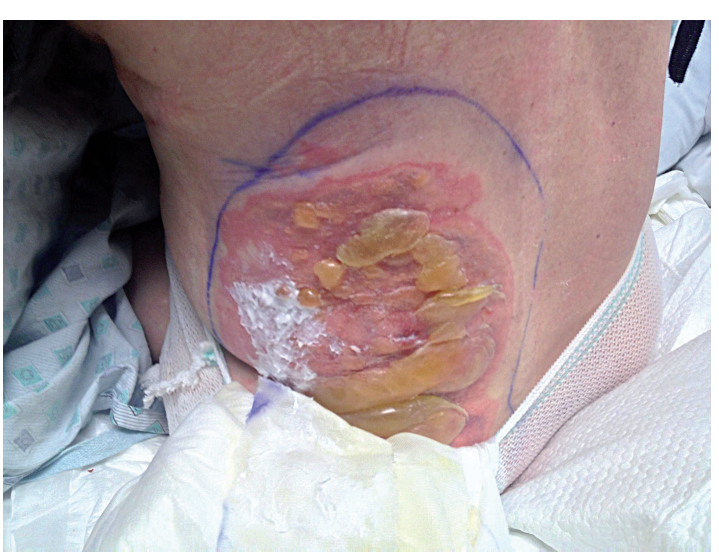
The patient returned to the ER five days later with increasing pain. Examination showed significant change in skin appearance with necrosis and eschar formation. The patient was hospitalized and underwent wound debridement for what was now recognized to be a full thickness skin burn. She was discharged home a week later with wound V.A.C therapy and a month later underwent successful split thickness skin grafting. Six months later, the flank area was well healed. She continues to experience pain which is treated with gabapentin.

Case 2 - The patient was an asymptomatic 60 years old female with a history of melanoma who underwent surveillance imaging and was incidentally found to have a 1.1cm left ureteropelvic junction renal calculus with significant hydronephrosis on CT scan. Other medical history included CVA, goiter, gallstones and psoriasis. Her medications included gabapentin, omeprazole, and lisinopril.

The patient underwent ESWL under general anesthesia using the same machine and coupling gel. As in the first patient, once in appropriate position with stone localized, 3,000 shocks were delivered at 120 shocks per minute and 24 kV. The machine was operated by the same technician as in the first case and once again the urologist was present throughout the procedure.

Upon removal of the lithotripter, a large raised erythematous area was noted on the left flank corresponding to the area of contact with the water-filled cushion. There were a few superficial bullae also visible (Figure-1). She was admitted and treated with daily silver sulfadiazine (Silvadene®) cream and Adaptic® dressings.

Figure 1 - Large raised erythematous area with superficial bullae seen on post-operative day 2.



CT scan of the abdomen performed on postoperative day 2 showed an intact stone with no fragmentation and minimal soft tissue stranding along the left flank. There was no evidence of injury to deeper organs. A decision was made to stent the left kidney and perform percutaneous nephrolithotripsy at a later date after complete healing of the flank burn. She was discharged home a week later.

The general surgery team involved in her care determined that approximately fifty percent of the injury was a full thickness burn. The patient refused operative debridement and skin grafting and continued daily wound care with collagenase Santyl® ointment mixed with Polysporin® and Adaptic® dressings. Five months later, she has had almost complete healing of the burn. No intervention for the calculus is planned until the wound is completely healed and stable for a period of time.

DISCUSSION

Complications following ESWL, immediate or delayed, can be infectious in nature, related to stone fragments, or due to the tissue effects of ESWL. These include bacteruria (7.7-23.5%) (1), sepsis (<1-2.7%) (1), hematuria, renal hematomas (2), and steinstrasse (2-10%) (3). Rare serious complications include injury to organs such as colon, small bowel, spleen, and liver. The most common skin injuries are petechiae and ecchymosis.

To our knowledge, this is the first report of full thickness skin burns following ESWL for renal calculi. There have been two previously reported cases of partial thickness skin burns following ESWL. One was of a first degree skin burn with erythema, bruising and slight pain which was treated with Thrombocid® (0.1%) (4). The second report by Sur et al. (5) was a case of a second degree skin burn following ESWL using a Medispec® EM1000 lithotripter. The patient had two renal calculi and a total of 4,000 shocks were delivered. Conventional ultrasound gel was used instead of the Medispec-recommended coupling medium, Lithoclear® gel. The authors speculate that the skin burns could be attributed to the number of shocks and bubbles associated with a nonapproved ultrasound gel or due to heat generated from the water-filled cushion. There were no mechanical defects in the specific lithotripter used.

In both our patients, a total of 3,000 shocks were delivered at 120 shocks per minute at a power of 24 kV. This is the number of shocks routinely delivered at our institution. Sonotech Clear Image Ultrasound gel® is the coupling medium routinely used with this particular machine. This specific lithotripter was evaluated by the parent company, Healthtronics®. The usual temperature inside the water-filled cushion is set at 36 degrees Celsius. It was discovered that the thermistor of the water-filled cushion was malfunctioning. Furthermore, it was found that the backup thermostat had faulty wiring. It was usually set to switch off when the water temperature in the shock head rose above 40 degrees Celsius. We presume that the increased water temperature in the cushion secondary to the malfunctioning thermostat was the cause of the skin burns, in the absence of any other explanation. Interestingly, this malfunction was discovered only after the second patient had suffered injury. In the interval between the two cases, the same technician had performed ESWL on seventeen other patients using the same lithotripter without incident. The lithotripter underwent trimesteral servicing even prior to the complication. Following these two incidents, the company has instituted safeguards to prevent future occurrences. The machine continues to be serviced every three months and both the thermistor and the thermostat are tested at each session.

The cause of the injuries in our report remains speculative. ESWL continues to have low morbidity more than 30 years after its initial implementation. Serious complications are rare and occur in less than 1% of patients. This report highlights an uncommon but serious complication of ESWL. We recommend an increased awareness of the possibility of this complication for medico-legal purposes. Proper preoperative patient counseling regarding the risk of rare but serious burn injuries will help to avoid potential litigation and malpractice claims.

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EDITORIAL COMMENT

Contrasting the reluctance of many journals to publish case reports these days, the vastness of cyberspace has allowed for the development of a new breed of medical journals, specialized in medical cases, allowing the publication and dissemination of notable case reports. While most are still in their infancy, these journals have the potential to act as large case banks.

Many publishers are now revisiting the important value of case reports and new case report specialized journals are surging in an increasing pace, expanding the room for simple reports with educational value, without compromising the classic journals impact factor.

Case reports usually describe an unusual or novel occurrence that though of anecdotal evidence, have a high sensitivity for detecting novelty and therefore remain one of the cornerstones of medical progress; also they provide many new ideas in medicine (1).

Additionally, case reports can have a tremendous impact on our daily practice, bringing a clear learning point, i.e. alerting others to an unexpected treatment response. In fact, the practice of medicine contains countless examples of elegant medical theories that contradict the best available evidence (2).

In the Editorial for the Challenging Clinical Cases Section announcement, I asked myself: "Why and what to write as "Challenging Clinical Cases" in the evidence based era?" (1).

Actually, one of the main roles of case reports is to call attention to a serious unexpected complication of a well-known treatment modality, which was nicely illustrated by surgical complications derived from a problem with the extra corporeal shockwave lithotripsy (SWL) machine thermostat presented by Rao et al. (3).

Though current lithotripters have alarms and sensors that will keep the operator aware of every malfunctioning item, such complications are worth mentioning during preoperative counseling and merit the attention of urologists when applying SWL. Also, recent guidelines or reviews on SWL should be amended to include remarks regarding skin burns as a SWL procedure rare serious complication.

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VIDEO SECTION

Vol. 40 (6): 858-859, November - December, 2014
doi: 10.1590/S1677-5538.IBJU.2014.06.20

Pure Laparoscopic Augmentation Ileocystoplasty

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ABSTRACT

Introduction: Guillain-Barre syndrome is an acute neuropathy that rarely compromises bladder function. Conservative management including clean intermittent catheterization and pharmacotherapy is the primary approach for hypocompliant contracted bladder. Surgical treatment may be used in refractory cases to improve bladder compliance and capacity in order to protect the upper urinary tract. We describe a case of pure laparoscopic augmentation ileocystoplasty in a patient affected by Guillain-Barre syndrome.

Presentation: A 15-year-old female, complaining of voiding dysfunction, recurrent urinary tract infection and worsening renal function for three months. A previous history of Guillain-Barre syndrome on childhood was related. A voiding cystourethrography showed a pine-cone bladder with moderate post-void residual urine. The urodynamic demonstrated a hypocompliant bladder and small bladder capacity (190mL) with high detrusor pressure (54 cmH2O). Nonsurgical treatments were attempted, however unsuccessfully.

The patient was placed in the exaggerated Trendelenburg position. A four-port transperitoneal technique was used. A segment of ileum approximately 15-20cm was selected and divided with its pedicle. The ileal anastomosis and creation of ileal U-shaped plate were performed laparoscopically, without staplers. Bladder mobilization and longidutinal cystotomy were performed. Enterovesical anastomosis was done with continuous running suture. A suprapubic cystostomy was placed through a 5mm trocar.

Results: The total operative time was 335 min. The blood loss was minimal. The patient developed ileus in the early days, diet acceptance after the fourth day and was discharged on the seventh postoperative day. The urethral catheter was removed after 2 weeks. At 6-month follow-up, a cystogram showed a significant improvement in bladder capacity. The patient adhered well to clean intermittent self-catheterization and there was no report for febrile infections or worsening of renal function. We did not experience any complication related to the intestinal anastomosis fully prepared intracorporeally.

Conclusions: Albeit technically challenging, pure laparoscopic enterocystoplasty was feasible and safe. Preparing the enteral anastomosis and the pouch intracoporeally may prolong surgical time and contribute to postoperative ileus. Surgical staplers can assist in the procedure, however they are not essential.

ARTICLE INFO

Available at: www.brazjurol.com.br/videos/november_december_2014/Reboucas_858_859video.htm

Int Braz J Urol. 2014; 40 (Video #15): 858-9

Submitted for publication:
October 04, 2014

Accepted after revision:
November 20, 2014

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EDITORIAL COMMENT

The video by Rebouças et al. nicely describes an augmentation ileocystoplasty performed entirely intracorporeally. This is a technically challenging surgery that requires advanced laparoscopic skills. When one contemplates performing more complex reconstructions laparoscopically, the potential benefits of laparoscopy must be weighed against the risks associated with prolonged operative times. Laparoscopic staplers and robotic assistance may help shorten surgical times, but they may also increase costs. Studies are currently underway to try to examine the results of intracorporeal urinary diversions. These investigations will help define the benefits and disadvantages of pure laparoscopic and robotic techniques (1).

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