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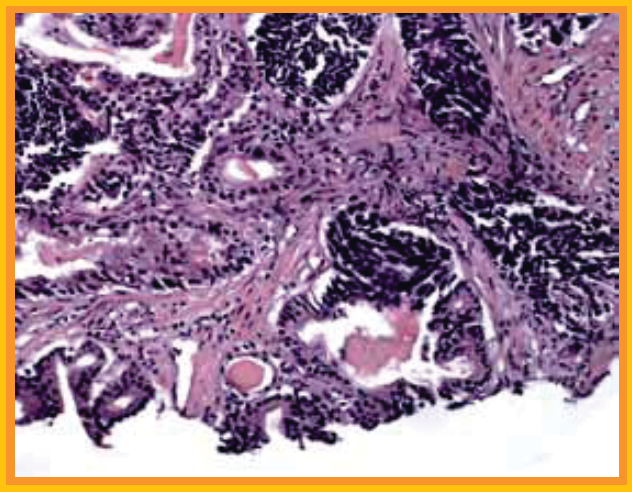

Neuroendocrine carcinomas of the prostate associated with an acinar component. (Page 600)

International Braz J Urol

EDITOR'S COMMENT

The September - October 2011 issue of the International Braz J Urol presents interesting contributions. The editor's comment highlights some of those papers.

Doctor Esteves and colleagues, from Brazil and USA, summarized the results from the current literature of sperm retrieval as well as the clinical outcome of ICSI in the clinical scenarios of obstructive and nonobstructive azoospermia (NOA). The goals of sperm retrieval are to obtain the best quality sperm possible in adequate numbers for immediate use and/or potential cryopreservation while minimizing the damage to the reproductive tract. Sperm production is normal and gametes can be easily retrieved from the epididymis or testis in cases of obstructive azoospermia (OA). In obstructive azoospermia, the choice of sperm retrieval by method and site of collection should be based upon preferences and expertise since there is no evidence that either percutaneous or microsurgery from either the testis or epididymis affects outcomes of sperm retrieval and assisted reproduction. Conversely, sperm production can be either markedly impaired or absent in men with nonobstructive azoospermia. The reproductive potential of azoospermic men candidates for sperm retrieval and ICSI is related to the type of azoospermia. The chances of retrieving spermatozoa and of achieving a live birth by ICSI are increased in couples whose male partner had obstructive rather than non-obstructive azoospermia.

Doctor Nardozza and colleagues, from Brazil, determined the pattern of blood testosterone concentrations decline with age in a cohort of 1,623 Brazilian healthy military men, aged from 24 to 87 years. The mean testosterone level was 575.5 ng/dL (25.0 to 1308.0 ng/dL). The evaluation of age-related changes in total testosterone levels revealed a progressive reduction in serum levels of this hormone with increasing age. Testosterone levels below 300 ng/dL were reported in 321 participants, a prevalence of nearly 20% in the study population. In agreement with other findings, a reduction of total testosterone levels with age was reported for healthy Brazilian men.

Doctor Deffontaines-Rufin and colleagues, from France, evaluated, retrospectively, the clinical and urodynamical response to the first BTX-A injection of patients suffering from refractory neurogenic detrusor overactivity (NDO) in Multiple sclerosis (MS). A total of 71 patients with MS underwent their first BTX-A injection for refractory NDO. They had clinical and urodynamic cystometry assessment before and 3 months after injection. Seventy seven percent of the patients had clinical improvement or full success of the treatment with a reduction of their urgency and incontinence. About 46% of the patients were in the "full success" group, 31% of the patients had a partial improvement and 23% of the patients had no efficacy of the treatment. Duration of MS was a predictive factor of treatment failure. The author concluded the injection therapy should be considered as soon as oral anticholinergic drugs fail to reduce NDO.

Doctor Pace and colleagues, from Italy, investigated whether specific plasma markers of inflammation and endothelial activation allowed discriminating BPH and PCa. A total of 45 patients were enrolled; 15 affected by BPH, 15 by PCa and 15 controls. Interleukin-6 (IL-6), CD40 ligand (CD40L), endothelial-selectin (E-selectin), platelet-selectin (P-selectin), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) were measured. In systemic blood samples, IL-6 has been found increased in patients affected by BPH (4.25 ± 0. pg/mL) and PCa (5.08 ± 0.24) respect to controls (2.62 ± 0.34; $p < 0.05$). CD40L was higher in BPH (4.25 ± 0.65 ng/mL; $p < 0.05$) than in control (2.31 ± 0.20) and PCa group (2.60 ± 0.56). E-selectin, P-selectin and VCAM-1 did not show any significant difference. Higher levels of ICAM-1 were detected in patients with PCa (573.04 ± 52.23)

and BPH (564.40 ± 74.67) than in the controls (215.30 ± 11.53 ng/mL; $p < 0.05$). In local blood samples, IL-6 has been found significantly increased in PCa in comparison with patients with BPH; there was no difference in CD40L, E-selectin, P-selectin, VCAM-1 ed ICAM-1. Based on their results the authors concluded that changes of inflammation and endothelial activation markers may be not considered of value in discriminating BPH and PCa.

Doctor Lima and colleagues, from Brazil, presented a study to asses the clinical and morphologic characteristics of neuroendocrine carcinomas (NEC) diagnoses in needle core biopsies. The study analyses 7 cases diagnosed on needle biopsies at a large tertiary regional cancer center from Northeastern Brazil. Two pathologists reviewed specimens retrospectively and demographic and morphologic characteristics were compared to 458 acinar tumors diagnosed in the same period. There were 5 small cell carcinomas and 2 low-grade neuroendocrine carcinomas (carcinoid). NEC were associated with an acinar component in 5/7 cases and the Gleason score of the acinar component was always > 6. The number of cores involved in prostates with NEC was greater (65% compared to 24% of acinar tumors, $p < 0.05$). The mean PSA at diagnosis was 417.7 (range 5.7-1593, SD 218.3), compared to 100.5 ($p = 0.1$) of acinar tumors (range 0.3-8545, SD 22.7). Prostates with NEC tend to be larger and involve a greater number of cores than acinar tumors. PSA at diagnosis does not seem to predict the presence of NE tumors in needle biopsy.

Dr. Miriam Dambros
Editor in Chief
International Braz J Urol

Review Article
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Sperm Retrieval Techniques for Assisted Reproduction

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ABSTRACT

Different surgical methods such as PESA, MESA, TESA, TESE and micro-TESE have been developed to retrieve spermatozoa from either the epididymis or the testis according to the type of azoospermia, i.e., obstructive or non-obstructive. Laboratory techniques are used to remove contaminants, cellular debris, and red blood cells following collection of the epididymal fluid or testicular tissue. Surgically-retrieved spermatozoa may be used for intracytoplasmic sperm injection (ICSI) and/or cryopreservation. In this article, we review the surgical procedures for retrieving spermatozoa from both the epididymis and the testicle and provide technical details of the commonly used methods. A critical analysis of the advantages and limitations of the current surgical methods to retrieve sperm from males with obstructive and non-obstructive azoospermia is presented along with an overview of the laboratory techniques routinely used to process surgically-retrieved sperm. Lastly, we summarize the results from the current literature of sperm retrieval, as well as the clinical outcome of ICSI in the clinical scenario of obstructive and non-obstructive azoospermia.

Key words: *infertility; male; azoospermia; sperm retrieval; reproductive techniques; assisted; review*
Int Braz J Urol. 2011; 37: 570-583

INTRODUCTION

Within the last decades there were two major achievements in the area of male infertility (1-3). The first was the introduction of intracytoplasmic sperm injection (ICSI) for the treatment of male factor infertility due to severely abnormal semen quality (1). The second was the extension of ICSI to azoospermic males and the demonstration that spermatozoa retrieved from either the epididymis or the testis were capable of normal fertilization and pregnancy (2,3). Azoospermia, defined as the complete absence of spermatozoa in the ejaculate after centrifugation, is found in 1-3% of the male population and in approximately 10% of the infertile males. Although azoospermia is associated with infertility, it does not necessarily imply sterility because many azoospermic men maintain sperm production at varying levels within the testes (4). Several sperm retrieval methods have been developed to collect sperm from the epididymis or the testis of azoospermic men. Surgically-retrieved spermatozoa can be used to induce pregnancy through assisted reproductive techniques (ART), i.e., in vitro fertilization associated to ICSI (1-7).

In this article, we review the methods for retrieval of epididymal and testicular spermatozoa and their success rates in different clinical conditions. We provide a critical appraisal of the advantages and limitations of the current surgical methods to retrieve sperm from male patients with obstructive (OA) and non-obstructive azoospermia (NOA). The reproductive potential of the male gamete extracted from the epididymis or the testis, and used for assisted fertilitization is also reviewed.

Evaluation of azoospermic patients prior to sperm retrieval.

The choice of sperm retrieval technique and its success rate is dependent on the type of azoospermia (obstructive or non-obstructive). Clinical history, physical examination and laboratory tests for endocrine assessment (serum follicle-stimulating hormone [FSH] and testosterone levels) are useful pre-operative diagnostic tools. Together, these factors provide a ~90% prediction of the azoospermia type (5). In OA spermatogenesis is intact but a mechanical blockage exists somewhere between the epididymis and the ejaculatory duct. Acquired OA include vasectomy, failure of vasectomy reversal, post-infectious diseases, surgical procedures in the scrotal, inguinal, pelvic or abdominal regions, and trauma (4,6). Congenital causes of OA include cystic fibrosis, congenital absence of the vas deferens (CAVD), ejaculatory duct or prostatic cysts and Young's syndrome (4-7). Nonobstructive azoospermia comprises a spectrum of testicular histopathology patterns resulting from various causes that include environmental toxins, medications, genetic and congenital abnormalities, varicocele, trauma, endocrine disorders, and idiopathic (4-7).

Men with OA usually have normal sized testes and hormone profile. Occasionally, the epididymis or the seminal vesicles may be enlarged or a cyst can be palpable on rectal examination. The presence of a low volume (< 1.5 mL) acidic (pH < 7.0) azoospermic ejaculate, with absent or low fructose and epididymal thickening, associated to nonpalpable vasa deferentia is pathognomonic of OA (4,6). Approximately two-thirds of men with OA and CAVD have mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Failure to identify a CFTR abnormality in a man with CAVD does not rule out the presence of a mutation, since some are undetectable by routine testing methods. The female partner should be offered CF testing before proceeding with treatments that utilize the sperm because of the high risk of the female being a CF carrier. If a CFTR gene mutation is identified (~4% of female partners are carriers), counseling is recommended before proceeding with sperm retrieval and ICSI due to the risk of the transmission of cystic fibrosis to the offspring (4,6-9). Azoospermic men with idiopathic obstruction and men with a clinical triad of chronic sinusitis, bronchiectasis, and obstructive azoospermia (Young's syndrome) may be at higher risk for CF gene mutations as well. In such cases, testing for CF mutations and counseling is also advisable (4,6).

Men with FSH levels, testicular size and ejaculate volume within normal ranges may have either NOA or OA (4, 6-9). In such cases, a testicular biopsy may be required to provide a definitive diagnosis. Histopathological evaluation of testicular specimens indicates the presence of normal spermatogenesis in cases of OA while hypospermatogenesis or maturation arrest or Sertoli cell-only (SCO) are seen in men with NOA. A testicular biopsy may be dismissed in cases of elevated FSH and small testes because this association is indicative of NOA (4,7). However, a biopsy may be considered to determine the likelihood of sperm retrieval in ICSI candidates with NOA. The presence of either spermatozoa on a wet prep or hypospermatogenesis on testicular histopathology is highly predictive of successful sperm retrieval in future retrieval attempts (8,10). Conversely, the absence of sperm in a biopsy specimen does not absolutely exclude the chances of finding sperm elsewhere within the testis due to the heterogenic distribution of spermatogenesis in NOA men (5,8,10).

Karyotyping and Y-chromosome microdeletion testing should be offered to men with NOA of unknown origin. Karyotypic abnormalities affect 10-15% of men with NOA, and the Klinefelter syndrome (KS) accounts for approximately two-thirds of the cases (8,11). Y-chromosome infertility is seen in 7-15% of men presenting with NOA. Genetic testing may provide prognostic information for sperm retrieval (5-8). Azoospermic patients with Y-chromosome microdeletions restricted to the AZFc region may harbor viable sperm within the testis. In contrast, the chances of finding sperm in men with complete AZFa or AZFb deletions is virtually zero (12,13).

WHAT ARE THE AVAILABLE SPERM RETRIEVAL TECHNIQUES?

In Table 1 we summarize the commonly used methods to retrieve sperm and their indications.

Table 1 - *Sperm Retrieval Techniques and their Indications for Assisted Reproduction.*

Technique	Acronym	Indications
Percutaneous epididymal sperm aspiration	PESA	OA cases only
Microsurgical epididymal sperm aspiration	MESA	OA cases only
Testicular sperm aspiration	TESA; TEFNA [1]	Failed PESA in OA Epididymal agenesis in CAVD cases Favorable testicular histopathology [2] in NOA Previous successful TESA attempt in NOA
Testicular sperm extraction (single or multiple biopsies)	TESE	Failed PESA or TESA in OA NOA cases
Microsurgical testicular sperm extraction	Micro-TESE	NOA cases only

OA: obstructive azoospermia; NOA: nonobstructive azoospermia
1 - Testicular fine-needle aspiration (TEFNA) is a technical variation of TESA; 2 - Hypospermatogenesis

Percutaneous Sperm Retrieval Methods

Craft and Shrivastav, in 1994, first described the use of the percutaneous approach to retrieve sperm from the epididymis (14). Two years later, Lewin et al. reported the use of testicular fine needle aspiration to retrieve sperm from the testis (15). Percutaneous retrievals are usually undertaken under local anesthesia only or in association with intravenous sedation. Percutaneous sperm retrieval can be either diagnostic or therapeutic. In the former, it is used to confirm the presence of viable spermatozoa prior to ICSI. In the latter, it is carried out at the same day of oocyte retrieval or at the day before.

Percutaneous Epididymal Sperm Aspiration (PESA)

For PESA, a fine needle (e.g, 26 gauge) attached to a 1 mL tuberculin syringe is inserted through the scrotal skin into the epididymis (Figure-1A). Negative pressure is created by pulling the syringe plunger while the tip of the needle is gently moved in and out inside the epididymis until a clear fluid is seen coming into the syringe. The amount of fluid aspirated is often minimal (~0.1 mL), except in cases of CAVD in which 0.3-1.0 mL may be obtained. The aspirate is flushed into a tube containing warm sperm medium. The tube containing the epididymal aspirate is taken to the laboratory for immediate microscopic examination (Figure-1C). PESA is repeated at a different site (from cauda to caput epididymis) until adequate number of motile sperm is retrieved. If PESA fails to retrieve motile sperm, testicular sperm retrieval can be attempted at the same operative time.

Testicular Sperm Aspiration (TESA)

Despite minor technical variations, the common principle of all methods described for TESA involves the needle insertion through the scrotal skin

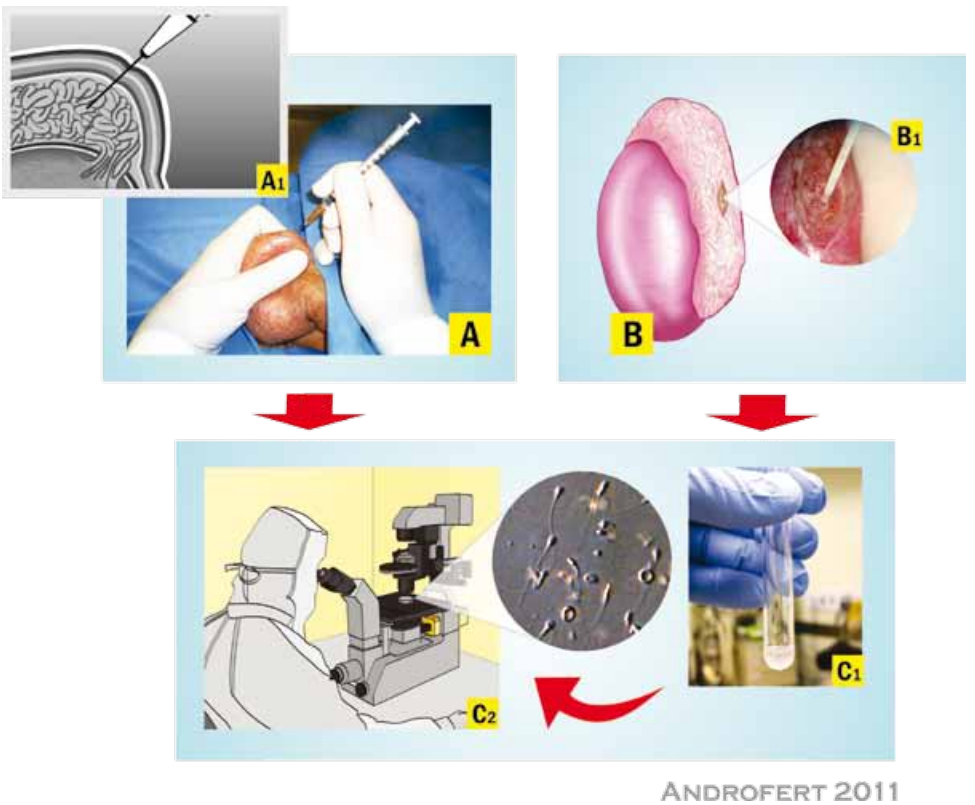

Figure 1 *- Epididymal Sperm Retrieval Techniques. A) Percutaneous Epididymal Sperm Aspiration (PESA). Epididymis is stabilized between the index finger, thumb and forefinger. A needle attached to a tuberculin syringe is inserted into the epididymis through the scrotal skin (A1), and fluid is aspirated. B) Microsurgical Epididymal Sperm Aspiration (MESA). After epididymis exposure, a dilated epididymal tubule is microdissected and opened. Fluid emanating from the epididymal tubule is aspirated using an angiocatheter attached to a tuberculin syringe (B1). C) Laboratory Sperm Handling. Aspirates are flushed into a tube containing HEPES-buffered sperm medium and sent for microscope examination (C1). Aspirate aliquots are spread onto a Petri dish and are examined microscopically to confirm the presence of motile sperm (C2).*

into the testis. Then, testicular parenchyma is percutaneously aspirated using fine (e.g. 22 gauge) or large diameter needle (e.g., 18 gauge). The needle is usually inserted at the anteromedial or anterolateral portion of the superior testicular pole, in an oblique angle towards the medium and lower poles. These areas are least likely to contain major branches of the testicular artery running superficially underneath the albuginea. Loupe-magnification may be used to avoid small vessels seen through the skin. Negative pressure is created by pulling the syringe plunger while the tip of the needle is moved in and out the testis in an oblique plane to disrupt the seminiferous tubules and sample different areas (Figure-2A). The specimen is flushed into a tube containing warm sperm medium, and is immediately transferred to the laboratory for microscopic examination (Figure-2C). TESA or TESE may be performed at the contralateral testis if insufficient or no sperm are obtained.

Microsurgical Sperm Retrieval Techniques

Microsurgical sperm retrieval can be performed under either local anesthesia in association with intravenous sedation or epidural anesthesia. Operating microscope and microsurgery techniques are used throughout the procedures.

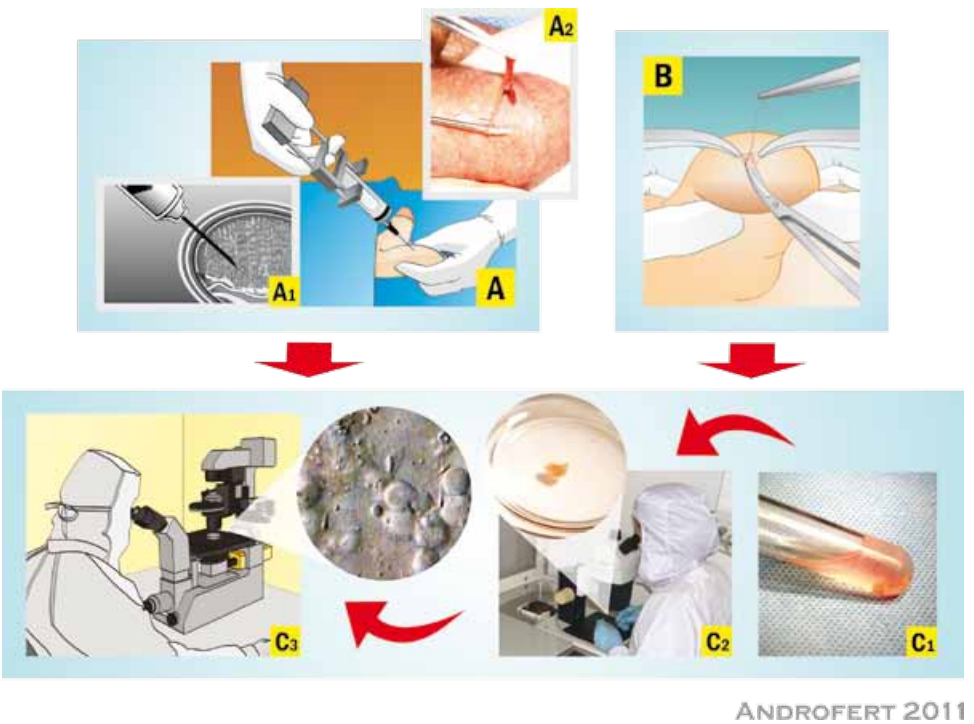

Figure 2 *- Testicular Sperm Retrieval Techniques. A) Percutaneous Testicular Sperm Aspiration (TESA). A needle attached to a syringe is percutaneous inserted into the testis. Negative pressure is created and the tip of the needle is moved within the testis to disrupt the seminiferous tubules and sample different areas (A1). A piece of testicular tissue is aspirated, and a forceps is used to remove the seminiferous tubules that exteriorize from the scrotal skin (A2). B) Conventional Testicular Sperm Extraction (TESE). A 1-2 cm skin incision is made to allow opening of scrotal layers down to the albuginea. Testicle is not exteriorized from scrotum. A small incision is made in an avascular area of the albuginea to expose testicular parenchyma. A fragment of approximately 5x5 mm is excised. Additional fragments may be taken from the same incision or from different testicular poles using multiple incisions. C) Laboratory Sperm Handling. Testicular specimens are flushed into a tube containing sperm medium (C1), and the tube is transferred to the laboratory for tissue processing. Testicular fragments are washed-free from blood clots, and seminiferous tubules are mechanically dispersed using needled-tuberculin syringes until no intact tubules are seen (C2). Testicular homogenates are microscopically examined to confirm the presence of spermatozoa (C3).*

Microsurgical Epididymal Sperm Aspiration (MESA)

MESA was first described by Temple-Smith et al. in 1985 (16). The surgical technique involves the exteriorization of the testis through a 2-3 cm transverse scrotal incision. The epididymal tunica is incised and an enlarged tubule is then dissected and opened with sharp microsurgical scissors. Fluid exuding from the tubule is aspirated with the aid of a silicone tube or blunted needle attached to a tuberculin syringe (Figure-1B). The aspirate is flushed into a tube containing warm sperm medium and is transferred to the laboratory for examination (Figure-1C). MESA is repeated at a different site of the same epididymis (from cauda to caput) and/or at the contralateral one until adequate number of motile sperm is retrieved. If MESA fails to retrieve motile sperm, TESA or TESE can be performed at the same operative time.

Microsurgical Testicular Sperm Extraction (micro-TESE)

Microsurgical-guided testicular sperm extraction was originally described by Schlegel in 1999 (17). The delivery of the testis is carried out as des-

cribed for MESA. Then, a single, large, mid-portion incision is made in an avascular area of the tunica albuginea under 6-8x magnification and the testicular parenchyma is widely exposed (Figure-3). Dissection of the testicular parenchyma is undertaken at 16-25x magnification searching for enlarged islets of seminiferous tubules (more likely to contain germ cells and eventually normal sperm production). The superficial and deep testicular regions may be examined, if needed, and microsurgical-guided testicular biopsies are performed by carefully removing enlarged tubules using microsurgical forceps. If enlarged tubules are not seen, then any tubule different than the remaining ones in size is excised. If all tubules are identical in appearance, random micro-biopsies are performed at each testicular pole. The excised testicular tissue specimens are placed into the outer-well Petri dish containing sperm media. Specimens are washed grossly to remove blood clots and are sent to the laboratory for processing and search for sperm (Figure-3). Albuginea and scrotal layers are closed using non-absorbable and absorbable sutures, respectively.

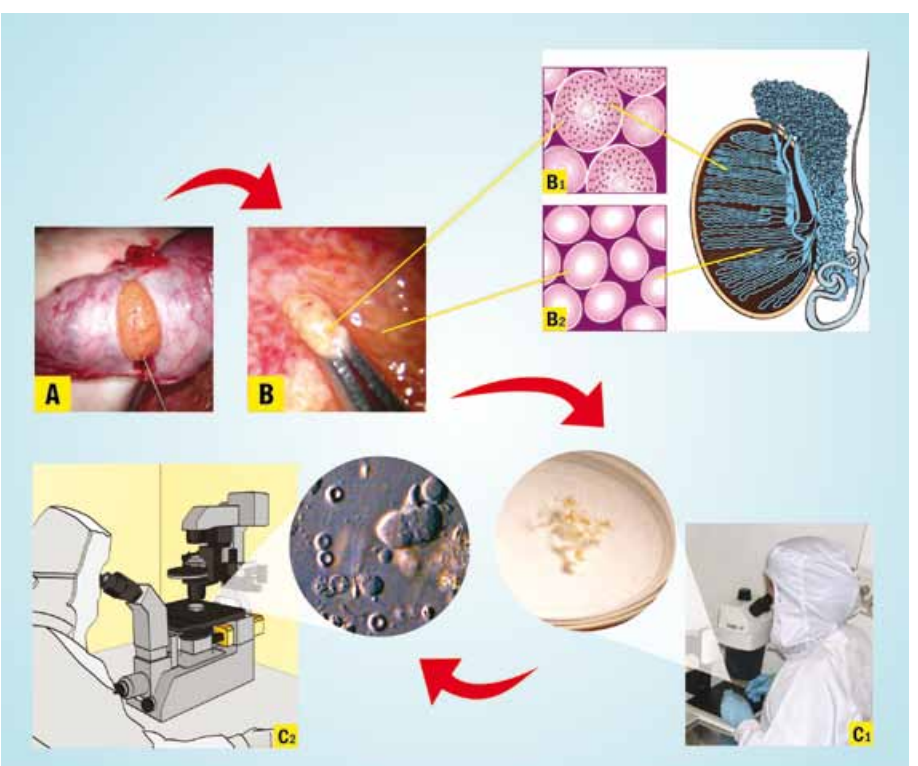

Figure 3 *- Microsurgical Testicular Sperm Extraction (Micro-TESE). Operating microscope and microsurgical technique are used throughout the procedures. After testis exteriorization, a single and large incision is made in an avascular area of the albuginea to expose testicular parenchyma (A). Microdissection of seminiferous tubules is carried out to identify and remove large tubules that are most likely to contain germ cells and active spermatogenesis. A photograph taken at x40-magnification indicates enlarged and non-enlarged seminiferous tubules (B). Enlarged tubules may contain active spermatogenesis, as illustrated in the transversal section of a histopathology specimen (B1). Non-enlarged tubules are more likely to contain no active spermatogenesis (B2). Excised testicular specimens are sent to the laboratory for processing and examination. Seminiferous tubules are mechanically dispersed using needled-tuberculin syringes (C1). Testicular homogenates are microscopically examined to confirm the presence of spermatozoa (C2).*

Conventional Testicular Sperm Extraction (TESE)

Extraction of testicular parenchyma for sperm search and their use in association with ICSI was first described by Devroey et al. in 1995 (3). For conventional TESE, a standard open surgical biopsy technique is used to retrieve sperm without the aid of optical magnification. TESE can be performed under either local anesthesia with or without intravenous sedation or epidural anesthesia, and it is often carried out using the 'window' technique. Briefly, a transverse 2 cm incision is made through the anterior scrotal skin, dartos and tunica vaginalis. A small self-retaining eyelid retractor is placed to improve exposure of the tunica albuginea, since the testis is not exteriorized. The albuginea is incised for approximately 1 cm. Gentle pressure is made onto the testis to extrude testicular parenchyma. A small fragment (approximately 5x5 mm) is excised with sharp scissors and placed promptly in sperm culture media (Figure-2B). A single specimen or multiple specimens can be extracted from the same incision. Alternatively, individual albuginea incisions can be made onto the upper, middle and lower testicular poles to extract multiple biopsy specimens. Testicular specimens are sent to the laboratory for processing and immediate microscopic examination (Figure-2C). Albuginea is closed using non-absorbable sutures.

Sperm Retrieval Postoperative Care and Complications

Percutaneous and open (microsurgical or conventional) sperm retrievals are usually carried out on an outpatient basis. Patients often resume their normal activities on the following day after percutaneous retrievals, and after 2-3 days following open surgical retrievals. Scrotal ice packing and scrotal supporter is recommended to decrease local edema and alleviate pain. Patients are counseled to restrain from ejaculation and strenuous physical activity for approximately 7-10 days. Oral analgesics and anti--inflammatory agents are usually prescribed because of the complaint of pain and scrotal swelling ranges from minimal to moderate.

The incidence of post-sperm retrieval complications ranges from 0-70% and include persistent pain, swelling, infection, hydrocele and hematoma (18-21). Complication rates vary according to the sperm retrieval technique and to a lesser extent to the type of azoospermia. PESA complications are usually of minimal morbidity although fibrosis at the aspiration site is often seen (6). Intratesticular hematoma has been observed in most patients undergoing TESE with single or multiple biopsies based on ultrasounds results performed after surgery, but they often resolve spontaneously without compromising testicular function (20). However, it has been reported that large-volume conventional TESE is associated with a higher risk of transient or even permanent decrease in serum testosterone levels due to testicular devascularization (19,22). The incidence of complications following micro-TESE is lower than conventional TESE (17,19,21,23). Using micro-TESE, identification of testicular vessels under the tunica albuginea is made prior to the placement of an incision into the testis. The use of optical magnification and microsurgical technique allow the preservation of intratesticular blood supply as well as the identification of tubules more likely to harbor sperm production (19). However, a significant decrease on serum testosterone has been documented following micro-TESE in men who already have diminished androgen production, such as KS patients (18). Nonetheless, testosterone levels return to the pre-surgical values in most individuals in a 12-month follow-up period. It is recommended that sperm retrievals should be performed by surgeons who have training in the procedures because of the potential serious postoperative complications (22).

LABORATORY PROCESSING OF SURGICALLY-RETRIEVED SPERM

Surgically retrieved-spermatozoa are often compromised in quality, particularly in the cases of NOA and after freezing and thawing (24). Therefore, great caution should be applied during processing of such specimens. In this regard, the laboratory has a crucial role not only to ease the sperm search and the selection of the best quality spermatozoa for ICSI but also to maintain the optimal sperm fertilizing ability (25). In order to achieve their goals, laboratory personnel should: i) receive the best quality surgically--retrieved specimen possible, with minimal or no

contaminants such as red blood cells and noxious microorganisms; ii) minimize iatrogenic cellular damage during sperm processing by mastering technical skills and controlling factors, such as centrifugation force and duration, exposure to ultraviolet light and temperature variation, laboratory air quality conditions, dilution and washing steps, quality of reagents, culture media and disposable materials; and iii) improve sperm fertilizing potential, if possible, by using stimulants (26) or selecting viable sperm for ICSI when only immotile spermatozoa is available (27).

Testicular specimens are processed by either mechanical mincing/shredding the whole tissue or enzymatic digestion. The aim of tissue processing is to facilitate sperm search, and both mechanical and enzymatic techniques yield similar results (28,29). After processing, epididymal and testicular spermatozoa can be either used for ICSI or cryopreserved. Cryopreserved specimens are thawed and processed using the principles already described (30). Methods for selecting viable sperm for ICSI are currently available in cases immotile spermatozoa only are obtained after processing (27,31).

SPERM RETRIEVAL SUCCESS RATES AND INTRACYTOPLASMIC SPERM INJECTION OUTCOMES

The best sperm retrieval technique for men with either OA or NOA is yet to be determined. Randomized controlled trials are lacking to compare the efficiency of the available methods and current recommendations are based upon cumulative evidence provided by descriptive, observational and controlled studies (7,9,22,23,32). The advantages and limitations of sperm retrieval techniques are shown in Table-2.

Obstructive Azoospermia

Both percutaneous and microsurgical methods yields high success rates, in the range of 90-100%, for obtaining spermatozoa in OA (6,9,33). It is recommended to commence aspiration at the corpus epididymis, and proceed to the caput if necessary, since aspirates from the cauda are usually rich in poor quality senescent spermatozoa, debris and macrophages (6). Epididymal sperm retrieval may fail in certain cases of epididymal fibrosis caused by multiple previous retrieval attempts or post-infection. In such cases, sperm retrieval can be attempted in the contralateral epididymis or in the testis (6). In a recent series of 142 men with OA, cumulative successful retrieval rate after percutaneous aspirations was 97.9% (33). Retrievals succeeded in approximately 86% of cases using PESA alone, although multiple epididymal punctures were required in nearly half of procedures. Rescue TESA yielded approximately 90% success rate in cases of failed PESA (33). In the aforementioned study, sperm retrieval success rates using percutaneous techniques were similar regardless of the cause of obstruction being vasectomy, CBAVD and post-infectious etiology categories.

The choice of sperm retrieval by either percutaneous or open surgery from either the testis or epididymis should be based upon local preferences and expertise since there is no evidence that the site or method of sperm retrieval affects outcome of ICSI for patients with OA (6,9,24,32). Moreover, neither the cause of obstruction nor the use of fresh or frozen-thawed epididymal/testicular sperm seems to have any significant effect on the success of assisted reproduction with regard to fertilization, pregnancy, or miscarriage rates (33-35). ICSI provides fertilization rates of 45-75% per injected oocyte when epididymal or testicular spermatozoa from men with OA are used. In such cases, clinical pregnancy and live birth rates reported in the recent literature range from 26-57% and 18-55%, respectively (24,35-38) (Table-3).

Non-obstructive Azoospermia

Recent series with NOA report overall successful retrieval rates (SRR) ranging from 30-50%. Testicular sperm have been obtained in all etiology categories of cryptorchidism, orchitis, genetic, radio-/chemotherapy and idiopathic (5,6,10,17,18,21,23). Efficiency of sperm retrieval in NOA males varies according to the method

Table 2 - *Advantages and Disadvantages of Sperm Retrieval Techniques for Assisted Reproduction.*

	Advantages	Disadvantages
PESA	Fast and low cost Minimal morbidity, repeatable No microsurgical expertise required Few instruments and materials No surgical exploration	Few sperm retrieved Cryopreservation limited Fibrosis and obstruction at aspiration site Risk of hematoma/spermatocele
MESA	Large number of sperm retrieved Excellent chance of sperm cryopreservation Reduced risk of hematoma Reconstruction possible [1]	Surgical exploration required Increased cost and time-demanding Microsurgical instruments and expertise required Postoperative discomfort
TESA	Fast and low cost Repeatable No microsurgical expertise required Few instruments and materials No surgical exploration Minimal/mild postoperative discomfort	Relatively low success rate in NOA Few sperm retrieved in NOA Cryopreservation limited Risk of hematoma/testicular atrophy
TESE	No microsurgical expertise required Fast and repeatable	Relatively low success rate in NOA Relatively few sperm retrieved in NOA Risk of testicular atrophy (with multiple biopsies) Postoperative discomfort
Micro-TESE	Higher success rates in NOA [2] Larger number of sperm retrieved [2] Relatively higher chance of sperm cryopreservation [2] Low risk of complications	Surgical exploration required Increased cost and time-demanding Microsurgical instruments and expertise required Postoperative discomfort

PESA: percutaneous epididymal sperm aspiration; MESA: microsurgical epididymal sperm Aspiration; TESA: percutaneous testicular sperm aspiration; TESE: conventional testicular sperm extraction; micro-TESE: microsurgical testicular sperm extraction.
1 - In cases of vasectomy; 2 - Compared to TESA and TESE in NOA

of sperm collection. TESA retrieval rates range from 10-30% (22,23,39-41), except in the favorable cases of previous successful TESA or testicular histopathology showing hypospermatogenesis. In such cases, TESA SRR range from 70-100% (6,10). In a recent systematic review the mean reported SRR for TESE was 49.5% (23). TESE with multiple biopsies resulted in higher SRR than fine-needle aspiration (TEFNA), a variation of TESA, especially in cases of Sertoli-cell-only (SCO) and maturation arrest (23). Retrieval rates ranging from 35% to 77% have been reported for micro-TESE

Table 3 - *Sperm Retrieval (SR) Success Rates and Intracytoplasmic Sperm Injection Outcomes (ICSI) Using Surgically-Retrieved Spermatozoa from Men with Obstructive and Nonobstructive Azoospermia.*

	Obstructive Azoospermia	**Nonobstructive Azoospermia**
SR Success Rates by Method; Mean (Range)		
Percutaneous	90% (80-100%)	35% (10-100%)
Microsurgical	90% (80-100%)	50% (20-100%)
ICSI Outcomes; Mean (Range)		
2PN Fertilization Rate	60% (45-75%)	50% (20-65%)
Clinical Pregnancy Rate	50% (26-57%)	30% (10-45%)
Live Birth Rate	35% (18-55%)	20% (8-35%)

(17-19,21,23,42,43). Current evidence suggests that micro-TESE performs better than conventional TESE or TESA in cases of maturation arrest and SCO, where tubules containing active focus of spermatogenesis can be identified (6,10,42). Moreover, tissue removal in micro-TESE is often 50 to 70-fold less than conventional TESE (17,43), and the small amount of tissue extracted facilitates sperm processing.

Preoperative predictive factors for sperm retrieval in NOA include testicular histopathology, serum FSH levels and genetic testing results (6,12,13,44). Although not absolute, testicular histology is still considered the best predictor for successful sperm retrieval in NOA. Retrieval rates of approximately 85% are obtained in men presenting with hypospermatogenesis while testicular sperm can be collected in only 6-25% of men with the unfavorable histopathology pattern of germinal aplasia (6,10,42,44). Follicle-stimulating hormone levels have also been used as a marker of testicular reserve, but it has been recently demonstrated that FSH levels in NOA men are not predictive of SRR (45,46). Although FSH levels reflect the global spermatogenic function, adequate feedback control from germ cells and Sertoli cells is usually intact in cases of diffuse maturation arrest despite the absence of sperm production (45). In genetic-related NOA, such as Y-chromosome infertility and Klinefelter syndrome (KS), pregnancies may be achieved by ICSI in males with retrievable testicular sperm (13,18). Testicular sperm can be found in approximately 70% of men with partial or complete AZFc deletion. In contrast, the chance of finding sperm in azoospermic men with complete AZFa or AZFb deletions is unlikely (8,12,13). In case a successful pregnancy is induced by men with Y-chromosome azoospermia, the male offspring will harbor the same deletion as their father, with a high risk of male infertility. In NOA men with KS, sperm are found in approximately 50% of cases on testicular exploration and pregnancy rates by ICSI range from 30% to 50% (18). It has been demonstrated that children that have been born have normal karyotype because germ cells in men with KS are euploid, 46,XY, and thus can form normal, haploid gametes (47).

The importance of surgical and medical treatment prior to sperm retrieval in NOA men has been recently highlighted. It has been suggested that treatment of clinical varicoceles prior to

sperm retrieval significantly increased the chance of testicular sperm collection by micro-TESE in NOA individuals with clinical varicoceles (48). In this aforementioned study, SRR rates were 53% and 30% in the treated and untreated men, respectively (odds-ratio [OR]: 2.63; 95% confidence interval [CI] of 1.05-6.60, p = 0.03). Medical therapy (aromatase inhibitors, clomiphene or human chorionic gonadotropin) prior to micro-TESE was also shown to enhance sperm retrieval success rates in Klinefelter syndrome men who responded to medication by increasing serum testosterone to more than 100 ng/dL from baseline (49).

Sperm retrieval may be performed either the day before or on the same day as the oocyte retrieval. Fresh sperm is preferable for ICSI because frozen-thawed surgically-retrieved sperm from NOA men have significantly impaired reproductive potential (50,51). From the limited data available, it is suggested that the sperm retrieval technique itself has no impact on ICSI success rates in NOA (23). However, ICSI provides lower fertilization rates per injected oocyte as well as clinical pregnancy and delivery rates when testicular spermatozoa from men with NOA are used in comparison to ejaculated sperm or epididymal/testicular sperm from men with OA (24,38,52) (Table-3). Such differences may be explained by the fact that testicular spermatozoa from men with severely impaired spermatogenesis have a higher tendency to carry deficiencies such as the ones related to the centrioles and genetic material, which ultimately affect the capability of the male gamete to activate the egg and trigger the formation and development of a normal zygote and a viable embryo (53).

The risks of congenital malformations, infertility and other diseases in children conceived by using surgically-retrieved sperm for ICSI are still poorly determined. Assisted reproduction techniques (IVF or ICSI), as a whole, are associated with multiple gestation and elevated risk of congenital abnormalities compared to the rate of malformations in children conceived naturally (1-4% rate) (54). ICSI, in particular, carries an increased risk of endocrine abnormalities as well as epigenetic imprinting effects (54,55). Although the absolute risk of any of these conditions remains low (54-56), current data is limited and it is therefore recommended that well-defined groups of ICSI with ejaculated sperm, ICSI with epididymal sperm and ICSI with testicular sperm, and a control group of naturally conceived children are closely followed-up.

CONFLICT OF INTEREST

None declared.

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Significant Heterogeneity in terms of Diagnosis and Treatment of Renal Cell Carcinoma at a Private and Public Hospital in Brazil

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ABSTRACT

Purpose: A great number of small renal lesions have now been detected. Nowadays, partial nephrectomy has more frequently been adopted for surgical treatment of earlier stage disease. Previous studies have associated patient, institutional, and health care system factors with surgery type. The aim of this study was to compare the diagnosis and treatment of renal cell carcinoma (RCC) according to hospital type, public versus private, in our country.

Materials and Methods: We retrospectively evaluated 183 patients with RCC who underwent radical nephrectomy or nephron-sparing surgery between 2003 and 2007 in two hospitals, one private and one public. Patient demographic, clinical, surgery, and pathologic characteristics were analyzed.

Results: The radical nephrectomy rate was higher at the public hospital than at the private hospital (75% vs. 57%, $p = 0.008$). Overall, patients at the public hospital presented larger tumors than did the patients who were cared for privately. Furthermore, small renal masses were significantly more prevalent in private care (57.8% vs. 28.3%). Patients at the public hospital showed a higher incidence of capsular invasion ($p = 0.008$), perirenal fat invasion ($p < 0.01$), lymph node involvement ($p < 0.001$), and a lower incidence of initial tumors. pT1 tumors were reported in 41% of patients at the public hospital and in 72% at the private hospital ($p < 0.001$).

Conclusion: Patients with RCC cared for at our public referral hospital showed a more advanced stage than RCC treated at the private institution.

Key words: nephrectomy; carcinoma; renal cell; neoplasm staging; prognosis
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INTRODUCTION

Approximately 200 000 new cases of renal cell cancer (RCC) are diagnosed all over the world every year, constituting the third most common genitourinary cancer, following bladder and prostate cancers (1). Indeed, RCC is one of the most lethal urological tumors; it is believed that 40% of RCC-diagnosed patients will die as a result of such disease, approximately 100 000 deaths per year all over the world (2). Moreover, the annual incidence of RCC has increased 2.5%, which is attributed at least in part to the widespread use of non-specific abdominal imaging (3,4). The current RCC series in literature shows that 60-70% of the patients are asymptomatic at the diagnosis (5). This change in the incidental presentation of renal mass doubled the prevalence of the localized disease from 1975 to 1995 (6,7). Paradoxically, despite diagnosis and early treatment, there has been an increase in the overall and disease-specific mortality rates in the last twenty years, according to SEER (Surveillance, Epidemiology, and End Results Program) database (8). In spite of

that, there are groups of patients with small, non-aggressive tumors which can be dealt with with conservative treatment or with only surveillance.

In Brazil there have been no data collected addressing the epidemiological profile of RCC. Therefore, the current incidence of incidental and symptomatic tumors and their respective staging and treatment is not known. The aim of this study was to evaluate the symptoms at diagnosis (incidental and symptomatic), the size of the tumors, the type of surgery performed (radical and conservative), the TNM stage and the anatomopathological characteristics of the sporadic RCC who are treated in two tertiary hospitals, one public and another private, in our country.

MATERIALS AND METHODS

We performed a retrospective study in which we reviewed prospectively collected data from 183 patients who underwent surgical treatment for RCC between July 2003 and December 2007 in two tertiary hospitals in Brazil. Ninety-three patients were treated at a public hospital (Hospital das Clínicas da Faculdade de Medicina de Sao Paulo), and ninety patients at a private hospital (Sociedade Beneficente de Senhoras Hospital Sírio-Libanês-Sao Paulo).

The data evaluated included the clinical presentation at the diagnosis (incidental or symptomatic), the type of surgery performed (conservative or radical) and anatomo-pathological characteristics (histological type, presence of sarcomatous differentiation, Furhman's nuclear grading system, presence of microvascular invasion, tumor size and TNM stage) 14. These characteristics were comparatively analyzed between the public and private hospital patients.

Postoperative follow-up included abdominal computed tomography and/or ultrasonography and hematological exams every four months during the two initial years, and every six months from the third to the fifth year. When the last consultation had taken place more than three months earlier, there was a telephone confirmation of the patient's current health condition.

For the statistical analysis the student's t-test and chi-square test were used. Results with p-values inferior to 5% ($p < 0.05$) were considered significant. Both institutions' review boards approved the study prior to accruing the patients, and informed consent was signed by all participants.

RESULTS

The median age was equivalent in both groups (56 vs. 60 years; $p = 0.204$). There was predominance of male patients at the private hospital compared to the public hospital (90% vs. 61. 3%; $p < 0.001$) (Table-1).

The diagnosis of the symptomatic tumors at the public hospital is 47.3% vs. 33.3% (Table-2). At the private hospital, there was a higher rate of patients with hematuria, whereas the public hospital showed a higher rate of patients presenting the classical triad (hematuria/pain/palpable mass). It is also worth noting that more patients presented metastatic disease at diagnosis at the public hospital when compared to the private hospital (Table-3).

The proportion of conservative surgery practically doubles at the private hospital ($p = 0.008$) (Table-2). The median tumor size was significantly different in both hospitals (Table-4): the median size was smaller than 4 cm at the private hospital and larger than 6 cm at the public hospital ($p < 0.001$). Another remarkable finding is that 58% of the tumors at the private hospital are smaller than 4 cm against only 28% at the public hospital ($p < 0.001$).

The pathological characteristics of the RCC in both hospitals are represented in Table-4. The public hospital patients presented locally advanced tumors, with higher percentage of capsular invasion ($p = 0.008$), perirenal fat invasion ($p = 0.01$), and presence of lymph node metastasis ($p < 0.001$). The percentage of pT1 tumors was higher at the private hospital than at the public hospital (72% vs. 41%; $p < 0.001$).

DISCUSSION

There were marked differences in the clinical presentation, type of surgery performed and histological findings of the RCC treated at public and private hospitals in Brazil. The median size of RCC detected at the private hospital was 2.4 cm, smaller than those

Table 1 *- Demographic data.*

		Hospital		
		Private (n = 90)	**Public (n = 93)**	**p-value**
Sex				< 0.001
	Female	9 (10.0%)	36 (38.7%)	
	Male	81 (90.0%)	57 (61.3%)	
Age				0.204
	Median (Q1-Q3)	56 (49 - 67)	60 (53 - 67)	
	Min - Max	23 - 87	20 - 91	

Table 2 *- Clinical presentation of RCC and type of surgery performed.*

	Hospital		
	Private (n = 90)	**Public (n = 93)**	**p-value**
Clinical Presentation			0.059
Incidental	60 (66.7%)	47 (52.8%)	
Symptomatic	30 (33.3%)	42 (47.3%)	
Surgery Performed			0.008
Partial	39 (43.3%)	23 (24.7%)	
Radical	51 (56.7%)	70 (75.3%)	

Table 3 *- Symptoms at diagnosis.*

	Hospital	
Symptoms	**Private**	**Public**
Hematuria	8 (8.6%)	47 (52.2%)
Pain	10 (10.7%)	28 (31.1%)
Weight Loss	-	6 (6.6%)
Metastasis	4 (4.4%)	7 (7.5%)
Palpable Mass	5 (5.5%)	8 (8.6%)
Hematuria / Pain / Palpable Mass	9 (10%)	13 (13.9%)
Others	7 (7.7%)	-

Table 4 *- Pathological characteristics.*

	Hospital		
	Private (n = 90)	**Public (n = 93)**	**p-value**
Character			0.997
Single	83 (92.2%)	71 (92.2%)	
Multiple	7 (7.8%)	6 (7.8%)	
Histological Type			< 0.001
Clear cells	62 (68.9%)	69 (86.3%)	
Bellini Duct	-	1 (1.3%)	
Papillary	20 (22.2%)	-	
Chromophobe	6 (6.7%)	8 (10.0%)	
Sarcomatous Degeneration	7 (7.8%)	4 (4.4%)	
Degree Fuhrman			0.627
Low (I and II)	58 (65.2%)	48 (61.5%)	
High (III and IV)	31 (34.8%)	30 (38.5%)	
Fat Invasion			0.011
No	79 (87.8%)	54 (72.0%)	
Yes	11 (12.2%)	21 (28.0%)	
Microvascular invasion			0.469
No	64 (71.1%)	42 (65.6%)	
Yes	26 (28.9%)	22 (34.4%)	
Capsular Invasion			0.008
No	71 (78.9%)	54 (60.7%)	
Yes	19 (21.1%)	35 (39.3%)	
Positive Lymph node			< 0.001
No	89 (98.9%)	19 (63.3%)	
Yes	1 (1.1%)	11 (36.7%)	
Renal Sinus invasion			0.331
No	24 (63.2%)	18 (75.0%)	
Yes	14 (36.8%)	6 (25.0%)	
Staging			< 0.001
T1	64 (71.9%)	38 (40.9%)	
T1a	52 (58,3%)	26 (28,1%)	
T1b	12 (13,6%)	12 (12,8%)	
T2	3 (3.4%)	21 (22.6%)	
T3	19 (21.3%)	28 (30.1%	
T4	3 (3.4%)	6 (6.4%)	
Tumor size (cm)			< 0.001
Median (Q1-Q3)	3.9 (2.6 - 5.5)	6.3 (4.0 - 10.8)	
Min - Max	1.2 - 14.5	0.8 - 24.0	
			< 0.001
≤ 4 cm	52 (57.8%)	26 (28.3%)	
> 4 cm	38 (42.2%)	66 (71.7%)	

detected at the public hospital. Nephron-sparing surgery was performed in half of the patients at the public hospital when compared to the private one. Furthermore, whereas approximately 60% of the patients operated on at the private hospital had tumors smaller than 4 cm, more than 70% of the public hospital patients presented tumor larger than 4 cm. pT1 RCC tumors occurred in 72% of the private hospital patients and in only 40% of the public hospital patients. Therefore, the fact that the public hospital is an academic teaching environment and the private is essentially a private practice probably did not play such an important role in determining the surgical approach in our study as did the tumor stage.

Differences in RCC histology between the groups reported in the present study may be associated with the disparate median tumor sizes. Patients with small renal masses (SRM) were probably less frequently referred to the public hospital, since it is a tertiary referral institution.

Radical nephrectomy was a rather common option in the public hospital, comprising 75% of renal surgeries, whereas at the private hospital, radical nephrectomy was performed in 57% of the cases. Long-term functional results for the patients who have undergone radical and conservative nephrectomy are very different . Lau et al. (9) have reported that the progression towards renal insufficiency (creatinine > 2 mg/dL) ten years after the renal surgery occurred in 22.4% of the patients who were submitted to radical nephrectomy versus 11.6% after partial nephrectomy.

RCC is a classically aggressive tumor; in clinical series from developed countries, one-third of the patients present metastasis at the diagnosis (10). Indeed, more than 40% of the RCC patients die due to that disease (11). The risk of death caused by RCC may be higher in developing countries like Brazil, especially in public hospitals. In our study, symptomatic and metastatic tumors comprised 47% and 15%, respectively, of the tumors treated at public hospitals and 33% and 4% of the tumors treated at private hospitals. In the United States, 25-30% of the patients initially present with metastatic RCC (12).

Today, more than 60% of RCC cases are incidentally detected in developed countries. (8,12-16). Nevertheless, in the present study, incidental diagnosis occurred in 67% of Brazilian private hospital patients and 53% of public hospital patients. Since the Brazilian public health system is based on universal coverage for approximately 203 million people, of which 68% have no private health insurance, medical visits and tests are often delayed due to long waiting lists (17).

The 2002 TNM presented a new proposal for the RCC stage, especially in T1 tumors (smaller than 7 cm, restricted to the kidney) (14). RCC stage T1 includes tumors with different outcomes. For instance, the likelihood of death within ten years for a patient with a 5- cm, low-degree RCC is less than 3%; however, a high-degree 5-7 cm RCC has a 40% likelihood of death in ten years (18). In Brazilian private and public hospitals approximately 72% and 41% of the patients presented stage pT1 tumors, respectively. Considering that life expectancy for T1 tumors is much higher, we can expect a higher RCC mortality at the Brazilian public institutions than at private hospital, a rather peculiar characteristic for our country. At the public hospital the classical triad (hematuria/pain/palpable mass), identified in 28% of the public hospital patients and 8% of the private hospital patients, respectively - can still be found.

An important limitation is that both are distinct pathology services and the surgeon's experience at the private hospital is higher. The data from public hospitals on diagnosis of metastatic disease are probably underestimated, and it is possible that data are actually higher.

Currently, renal masses are detected incidentally, with smaller sizes constituting the ideal cases for conservative surgery (19,20). However, recent series from developed countries showed that conservative kidney surgery has been underutilized; only 9.6% of the surgeries carried out due to RCC are conservative (21). In this context, our study showed that nephron-sparing surgery was carried out in 43% and 24% of private and public hospital individuals, respectively. Although not

broadly representative, these two particular hospitals may indirectly reflect the patterns of care in the private and public health systems in Brazil. Nonetheless, an external validation of these findings is needed to confirm this discrepancy.

CONCLUSIONS

Patients with RCC operated on at a tertiary public hospital in Brazil showed a more technically advanced histopathological evaluation than those treated at a private institution, reflecting the different standards of treatment that patients may undergo according to their socioeconomic level.

CONFLICT OF INTEREST

None declared.

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Age-related testosterone decline in a Brazilian cohort of healthy military men

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ABSTRACT

Introduction: Androgen decline in the aging man has become a topic of increasing clinical relevance worldwide, as the reduction in testosterone levels has been reported to be accompanied by loss of muscle mass, accumulation of central adiposity, impaired mobility and increase risk of bone fractures. Although well-established in studies conducted in developed countries, progressive decline in serum testosterone levels with age has been poorly investigated in Brazil.
Aim: To determine the pattern of blood testosterone concentrations decline with age in a cohort of Brazilian healthy military men.
Materials and Methods: We retrospectively reviewed data on serum testosterone measurements of healthy individuals that had undergone a routine check-up at the Military Biology Institute. Blood samples were obtained early in the morning, and total testosterone concentration was determined using a commercial chemoluminescent immunoassay. Mean values were analyzed in five age groups: ≤ 40, 41 to 50, 51 to 60, 61 to 70, and > 70 years.
Main Outcome Measure: Mean total testosterone levels.
Results: 1,623 subjects were included in the analysis; mean age was 57 years (24 to 87), and mean testosterone level was 575.5 ng/dL (25.0 to 1308.0 ng/dL). The evaluation of age-related changes in total testosterone levels revealed a progressive reduction in serum levels of this hormone with increasing age. Testosterone levels below 300 ng/dL were reported in 321 participants, a prevalence of nearly 20% in the study population.
Conclusion: In agreement with other findings, a reduction of total testosterone levels with age was reported for healthy Brazilian men.

Key words: *testosterone; male; deficiency; epidemiological studies; cohort studies*
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INTRODUCTION

Over the last decades, an increase in life expectancy has been observed worldwide (1). In addition, population projections indicate that the world population will experience a marked increase in the proportion of individuals older than 65 years. According to the United Nations, the percentage of the world's population over 60 is expected to nearly double between 2005 and 2050 (2). In this context, projections for the Brazilian population estimate an increase in the number of men older than 60 years, from 9 million (representing 9% of the total country population) to 30 million (13%), between 2010 and 2020 (3). Despite the fact that males do not live as long as females, the health of aged men has been studied to a much lesser extent than that of postmenopausal women. Thus, growing attention is being devoted to health disorders in aging men.

Aging in men is associated with impaired mobility, accumulation of central adiposity, decreased lean body and muscle mass, strength, and bone mineral density, as well as increased body fat (4), abnormalities that are also present in non-elderly hypogonadal men. Unlike women, who experience a dramatic change in sex-hormone profile during menopause (5), age-related changes in reproductive hormones occur gradually throughout the years of life in men (6,7). As the alterations in hormonal status are subtle, the characterization of age-normal endocrine profile is particularly difficult in males.

It is well-established that after the fourth or fifth decade of life, men undergo a gradual shift in the levels of important sex hormones, with a rise in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex-hormone-binding globulin (SHBG), contrasting with a decline in testosterone and dehydroepiandrosterone (DHEA) (8-11). It has been estimated that from the age 19, circulating testosterone declines at an average rate of 1% per year of life, or 100 ng/dL (4,7,8).

Several age-related phenomena such as decrease in muscle strength and mass, decline in virility and sexual activity, and impairment of glucose metabolism have been associated with a reduction in testicular function in aging men (12). The extent to which declining testosterone levels may influence age-related deteriorations is not completely defined. In addition, androgen deficiency in the aging male (ADAM) is characterized by the presence of a group of signs and symptoms and a significant decline in the production of hormones, most importantly testosterone.

Age-related decline in testosterone levels has been demonstrated by several cross-sectional and longitudinal studies conducted in developed countries (4,11). However, data on the androgen profile of aging men are scarce for Brazil.

Aim

The aim of the present study was to investigate the age-related decline of total testosterone levels in healthy Brazilian men in military activity.

MATERIALS AND METHODS

Study design

In this retrospective study, data on testosterone levels of healthy military subjects were reviewed. Blood samples were collected from January 2009 to September 2009 at the Military Biology Institute ("Instituto de Biologia do Exército" - IBEX), located in Rio de Janeiro, Brazil, as part of a routine health check-up that was mandatory for military individuals in activity or retired at that time. The study was designed to collect demographic and laboratory parameters of healthy men, age 18 or older, in activity at the military service or retired. All individuals with available hormone measurements were included.

The patients were not on testosterone replacement therapy. They were not taking medications that affect testosterone level, such as clomid or HCG injections, nor were they taking antiandrogens such as cimitidine, Aldactone, etc. They had not undergone previous surgery e.g. orchiectomy, nor had they received chemotherapy or radiation on the testis. They did not have chronic liver disease or liver cell failure, nor did they suffer from morbid obesity, DM, or chronic illness.

Laboratory measurements and statistical analysis

Blood samples were obtained early in the morning, between 7:00 and 09:30 AM, and analyzed at the IBEX laboratory. Serum was immediately separated after blood collection and samples were stored at -80°C. Total testosterone level was measured using a commercial chemoluminescent immunoassay, with an analytical sensitivity of 300 to 1000 ng/dL. Data collected from each subject included age and mean total testosterone levels. Laboratory testosterone levels compatible with hypogonadism were defined as < 300 ng/dL, based on the guidelines for ADAM of the Brazilian Society of Urology.

Participants' total testosterone levels were used for analysis, and mean values were analyzed

regarding the age groups. For this purpose, subjects were divided in the following age groups: ≤ 40, 41 to 50, 51 to 60, 61 to 70, and > 70 years.

RESULTS

Sample characteristics

A total of 1623 healthy subjects were evaluated in the present study. Demographic and laboratory data of all individuals included in the analysis are summarized in Table-1. The mean age was 57 years, ranging from 24 to 87 years. Mean total testosterone level was 575.5 ng/dL, ranging from 25.0 to 1308.0 ng/dL. Concerning the distribution of participants according to different age groups, 13.6% were ≤ 40 years, whereas the majority of subjects were older than 50 years, as shown in Table-2.

Testosterone measurements according to age

In order to evaluate age-related changes in total testosterone levels, the concentration of this hormone was analyzed in the different age groups, as shown in Figure-1. In this regard, a progressive reduction in serum total testosterone levels was observed across age groups, with the mean testosterone value observed for younger men (821.1 ng/dL; age group ≤ 40 years) being almost twice as high as the levels found for individuals belonging to the older age group (436.6 ng/dL; age group > 70 years).

Figure-2 shows the distribution of participants according to the mean testosterone level groups. Although the study sample consisted of apparently healthy individuals, 0.8% of the subjects had testosterone levels ≤ 100 ng/dL, 3.6%

Table 1 *- Characteristics of the 1,623 participants included in the analysis.*

Characteristics	Value
Age (years)	
Mean	57.0
Range	24 to 87
Total testosterone levels (ng/dL)	
Mean	575.5
Range	25.0 to 1308.0

Table 2 *- Distribution of subjects according to age groups.*

Age group (years)	Number of subjects (%)
≤ 40	221 (13.6)
41 to 50	312 (19.2)
51 to 60	448 (27.6)
61 to 70	512 (31.6)
> 70	130 (8.0)
Total	**1623**

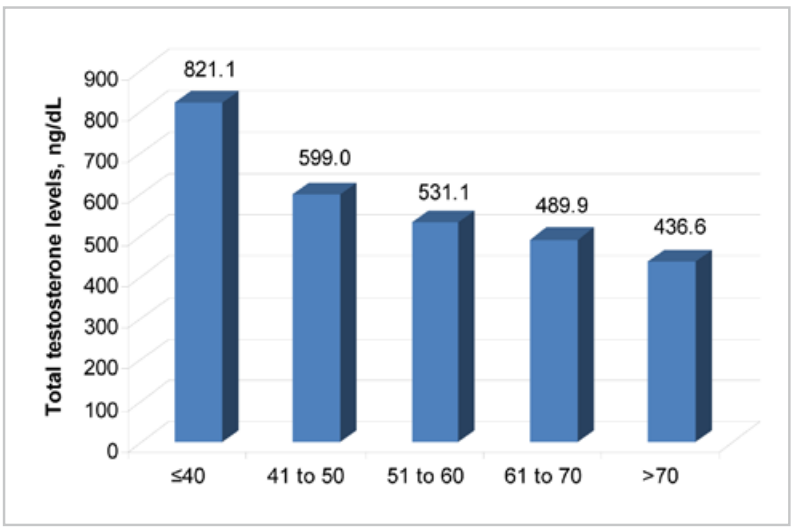

Figure 1 - *Age groups.*

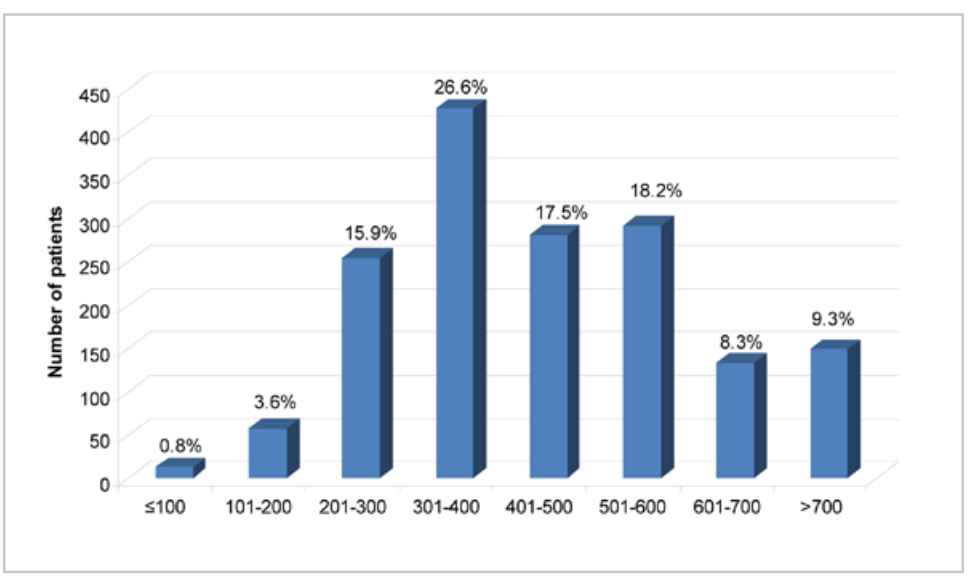

Figure 2 - *Testosterone level groups. (ng/ dL)*

had mean levels between 101 and 200 ng/dL, and 15.9% of participants had a mean concentration of this hormone in the range of 201 and 300 ng/dL. Testosterone levels below 300 ng/dL, compatible with hypogonadism, were reported for 321 participants, representing a prevalence of 19.8%.

DISCUSSION

In this study, the hormone profile of a cohort of healthy Brazilian men in military activity was investigated. We found, in agreement with the current literature, a decline in total testosterone levels associated with male aging.

Testosterone is largely bound to plasma proteins, with only 1-2% being free, 40-50% being bound to albumin, and the rest being strongly bound to SHBG (12). Plasma concentrations of this androgen show circadian variations with highest values in the morning, and serum free testosterone and albumin-bound testosterone represent the fractions readily available for biological action (13). As testosterone exerts a wide

role in male physiology, controlling gonadal function and altering libido, mood, aggressive behavior, liver function, muscle mass, bone formation, lipid metabolism, erythropoiesis, and immune system, its decline is of particular concern in the management of men's health (14).

In men, a progressive decline in testosterone levels with age has been suggested in several cross-sectional and longitudinal studies, with an average rate of decline of 1% to 2% per year after the age of 40. In addition, data indicate that a significant percentage (20%) of men over 60 years exhibit serum levels below the lower limits of young men. Moreover, at the age of 75 years, mean total serum testosterone level was found to be about two-thirds of the levels at age 25, whereas the mean values of free and bioavailable testosterone serum levels are only about half of those in young men, as demonstrated in different studies (4,8,15,16). In addition to changes in total testosterone, a decline in free and bioavailable testosterone has been demonstrated in cross-sectional studies.

Morley et al. demonstrated in a longitudinal study, conducted in older healthy men (61 to 87 years at entry), that testosterone levels decline with age, with an average rate of decrement of 110 ng/dL for every decade of life. In addition, LH and FSH were found to increase in older men (7). Longitudinal changes in androgen hormones have been also reported in more recent studies. In this regard, using longitudinal data from the Massachusetts Male Aging Study (MMAS), which included at baseline a large cohort of men aged 40 to 70 years. Feldman et al. reported a rate of decline in total testosterone with age of 0.8% per year, and a declining rate of 2.0% per year for both free and albumin-bound testosterone. Of note, in this study the rate of decline was similar in apparently healthy men and in those reporting obesity, chronic illness, alcoholism, prostate problems, or prescription medication (8). In another longitudinal study, Liu et al found that the decline in serum testosterone and increase in SHBG with age were comparable across two separate regional Australian populations (11). The influence of age in the testosterone levels was confirmed by Clapauch et al. in a study conducted in a cohort of 216 Brazilian men aged 52-84 years (17). In this study, a significant difference in the level of total testosterone was observed between patients < 60 years versus those aged 70 years or more. In addition to total testosterone, a significant difference in free testosterone levels was also observed between these two age groups (17).

In young patients, severe testosterone deficiency (170 to 230 ng/dL) is typified by a familiar array of symptoms, whereas in aging men, symptoms are non-specific and usually mimicked by other disorders. In older men, the testosterone level below which symptoms of androgen deficiency emerge remains unclear (18,19).

Adult hypogonadism can be caused by abnormalities of the hypothalamic-pituitary-testicular axis at the testicular level causing primary testicular failure, or by disturbances of the hypothalamus or pituitary resulting in secondary testicular impairment. Adult hypogonadism is manifested by infertility, alterations in behavior, low sexual desire, erectile dysfunction, depression, fatigue, loss of sense of well-being, and some secondary sexual characteristics (18,20). Obesity, severe systemic illness and medications are among the commonly acquired causes of adult-onset hypogonadism, and defects in both testicular and hypothalamic-pituitary function may underlie the age-associated reductions in testosterone levels demonstrated in cross-sectional and longitudinal studies. In our sample, testosterone levels compatible with hypogonadism (< 300 ng/dL) were observed in almost 20% of the participants. Although this concentration is not diagnostic of hypogonadism per se, it may indicate the need of preliminary screening for free or bioavailable testosterone levels below references values. Recently, Wu et al. found, in a systematic investigation of a large cohort of aging men from the general population, that late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone concentration lower than 11 nmol per liter (320 ng/dL) and a free testosterone level of less than 220 pmol per litre (64 pg/mL) (18).

Although an improvement in signs and symptoms of testosterone deficiency in younger adult men is supported by some studies, the treatment of testosterone deficiency in the older man is more controversial. Recently, an update of the guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men was published,

recommending that the diagnosis of androgen deficiency should be restricted to men with consistent symptoms and signs and low serum testosterone levels (21). In this regard, the analysis of morning total testosterone levels is indicated as the initial diagnostic test, which should be confirmed in a repeated measure (21). In this guideline, testosterone therapy is recommended for men with symptomatic deficiency of androgens, aiming to maintain secondary sex characteristics and to improve sexual function, well being, and bone density, with the exception of patients with breast or prostate cancer, and other health conditions not mentioned here. Importantly, there is a recommendation against androgen deficiency screening in the general population. Regarding the elderly population, for older men with consistent low testosterone levels and clear clinical symptoms of androgen deficiency, testosterone therapy should be considered by clinicians on an individualized basis, considering the risks and benefits of this therapeutic approach (21). The effects of testosterone administration on body composition, bone density and muscle strength in middle-aged men were evaluated in a meta-analysis of randomized controlled trials. Testosterone treatment promoted reduction of body fat, increase in fat-free mass, with no change in body weight. In addition, testosterone also reduced total cholesterol, with no change in low density lipoprotein-cholesterol (22). Despite some good results, whether testosterone therapy is beneficial for aging men in preventing or delaying some aspects of ageing is still controversial, and more studies are needed (23,24).

CONCLUSIONS

In agreement with other studies we found that total testosterone levels decline with age in healthy Brazilian men. A high prevalence of testosterone levels below 300 ng/dL, compatible with laboratory hypogonadism, was found in this cohort.

CONFLICT OF INTEREST

None declared.

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Prostatic carcinomas with neuroendocrine differentiation diagnosed in needle biopsies, a morphologic study of 7 cases among 465 sequential biopsies in a tertiary cancer center

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ABSTRACT

Purpose: Neuroendocrine carcinomas (NEC) of the prostate are rare, with only a few series hitherto reported. The objective of this study was to assess in a single institution the clinical and morphologic characteristics of neuroendocrine carcinomas diagnosed in needle core biopsies.
Materials and Methods: The current study analyses seven cases diagnosed in needle biopsies at a large tertiary regional cancer center from Northeastern Brazil. Two pathologists reviewed specimens retrospectively, and demographic and morphologic characteristics were compared to 458 acinar tumors diagnosed in the same period.
Results: There were five small cell carcinomas and two low-grade neuroendocrine carcinomas (carcinoid). NEC were associated with an acinar component in 5/7 cases and the Gleason score of the acinar component was always > 6. The number of cores involved in prostates with NEC was greater (65% compared to 24% of acinar tumors, $p < 0.05$). The mean PSA at diagnosis was 417.7 (range 5.7-1593, SD 218.3), compared to 100.5 ($p = 0.1$) of acinar tumors (range 0.3-8545, SD 22.7). Prostates harboring NEC were bigger ($p < 0.001$, mean volume 240 mL vs. 53 mL of acinar tumors). Treatment of NEC included palliative surgery, chemotherapy, and hormonal therapy.
Conclusions: NEC of the prostate is rare and often associated with a high-grade acinar component. Prostates with NEC tend to be larger and involve a greater number of cores than acinar tumors. PSA at diagnosis does not seem to predict the presence of NE tumors in needle biopsy.

Key words: *prostate; neoplasms; carcinoid tumor; neuroendocrine tumor; treatment outcome*
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INTRODUCTION

Neuroendocrine carcinomas (NEC) of the prostate are rare, representing less than 0.5% of prostate carcinomas in the few series reported to date (1-8). The current classification of neuroendocrine carcinomas is based on the World Health Organization 2004 lung tumor classification, and it divides those tumors into well-differentiated neuroendocrine carcinomas (carcinoid tumors), moderately-differentiated neuroendocrine carcinomas (atypical carcinoid tumors), and poorly-differentiated neuroendocrine carcinomas, which include two morphologic distinct entities (small cell carcinomas and large cell neuroendocrine carcinomas) (9). The classification is based solely on histomorphology and relies on both light microscopy and immunohistochemical studies.

Albeit rare, the most common neuroendocrine carcinoma of the prostate is by far small cell carcinoma. Furthermore, it is estimated that up to 10% of prostate cancer in patients with androgen-resistant disease after long-term androgen deprivation therapy are high grade NEC, most with associated acinar adenocarcinoma (10).

Recognition of this entity via needle biopsies is critical, as its therapy differs significantly from that of usual acinar high-grade prostatic adenocarcinoma.

MATERIALS AND METHODS

Seven cases of neuroendocrine carcinomas primary to the prostate were collected over 4 years (2006-2010) from the Department of Pathology archives of the Cancer Hospital of the Ceara Cancer Institute among 465 sequential needle biopsies from the in-house Urology Department Service. Patients with neuroendocrine tumors primary to other sites were excluded from the study.

The morphologic data independently collected and reviewed by two pathologists (FT and CDM) were basic morphology to include small or non-small cell pattern, percentage of cores involved, association with conventional acinar adenocarcinoma and the Gleason grading, mitotic rate, presence of tumor necrosis and any other morphologic findings.

Immunohistochemical studies were performed on the available paraffin blocks in all seven cases. Immunohistochemistry was performed in our laboratory using the standard streptavidin-biotin-peroxidase procedure. Primary monoclonal antibodies to PSA (dilution 1:100), chromogranin (1:2000), synaptophysin (1:50), ki67 (1:100) and p63 (1:300) (Dako Inc., Carpinteria, USA) were applied to 5-mm thick 10% formalin-fixed, paraffin-embedded tissue sections. The sections underwent a process of deparaffinization, rehydration, and washing in xylene, graded alcohols, and distilled water. Blockage of endogenous peroxide activity was performed by incubation with 3% H_2O_2. The sections were placed in 10 mM citrate buffer at pH 6 with subsequent antigen retrieval procedure. The antigen-antibody reaction was visualized using the avidin-biotin peroxidase complex and diaminobenzidine as the chromogen. Slides were counterstained with hematoxylin. Positive results consisted of dark brown nuclear (p63, ki67) and cytoplasmic (chromogranin, synaptophysin) staining and cytoplasmic and luminal granular staining of secretory epithelial cells by PSA. Appropriate positive and negative controls were included. Only staining that was moderate or strong was considered positive.

Clinical follow-up was possible in all but one case by retrospective clinical chart review by one of the authors (MVL).

Clinical and histopathologic variables were compared among categorized groups using the χ^2 test or Student t- test. A p value less than 0.05 was considered significant. The software SPSS 5.0 (Chicago, IL) was used for statistical analyses.

RESULTS

The clinical and pathological characteristics of the seven cases are summarized in Tables 1 and 2. Those cases were retrieved spanning four years and included all needle biopsies performed at the Urology Department at our institution among 465 sequential biopsies (1.5%). The mean age at diagnosis was 69.8 years. Metastatic NEC from any other site or direct extension from the bladder or gastrointestinal tract were excluded clinically in all cases. The serum PSA values at the time of initial diagnosis were available in 5 patients and ranged from 7.3 to 1449.0 ng/mL (mean 461.1 ng/mL, median 194.15 ng/mL).

There were five small cell carcinomas and two tumors with morphology and mitotic count compatible with low-grade neuroendocrine carcinomas (carcinoid). There was no significant difference in tumor extent in biopsies between small cell carcinomas and carcinoid tumors. The numbers of cores obtained in the needle biopsies diagnosed with prostatic neuroendocrine tumors were six in two cases, eight cores in four cases and 12 cores in one case. NEC were associated with an acinar component in five of seven cases and the Gleason score of the acinar component was always > 6 (Figures 1-3). One patient had a Gleason score of 3+4, a second 4+4, and a third 5+4 (Table-1). The five tumors with associated acinar adenocarcinomas in the biopsies involved a higher number of cores than the two tumors without an acinar component, but the difference was not significant. NEC tended to fragment in needle cores, and histologic crush artifact was also a common feature (Figure-4). Tumor necrosis was common and present at least focally in six of seven cases (Figure-5). Cytologically, tumor cells were small, with scant cytoplasm and open chromatin, with inconspicuous nucleoli (Figure-6). Immunohistochemical findings included positivity for neuroendocrine epitopes (chromogranin and synaptophysin) in all tumors with varying degrees of positivity. Chromogranin was stronger overall. The Ki-67 proliferative index varied from 40 to 90% in

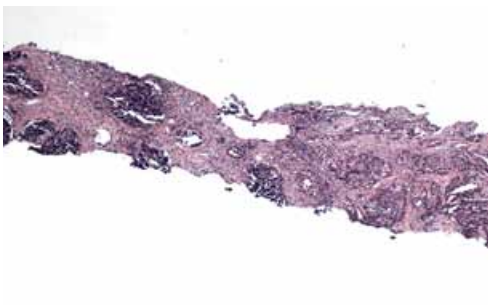

Figure 1 - *Low power of small cell carcinoma (left) associated with Gleason 8 acinar adenocarcinoma (right). Hematoxilin-eosin, 40x.*

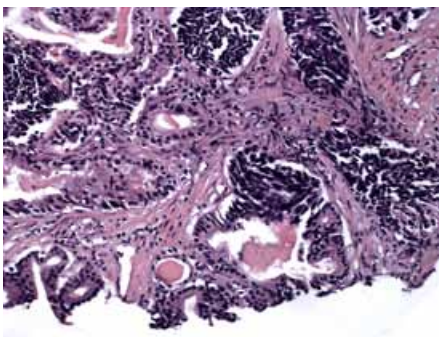

Figure 2 - *Small cell carcinoma associated with acinar adenocarcinoma. On the upper right corner, small cell carcinoma predominates, whereas acinar Gleason pattern 3 can be seen in the left lower corner. Hematoxilin-eosin, 200x.*

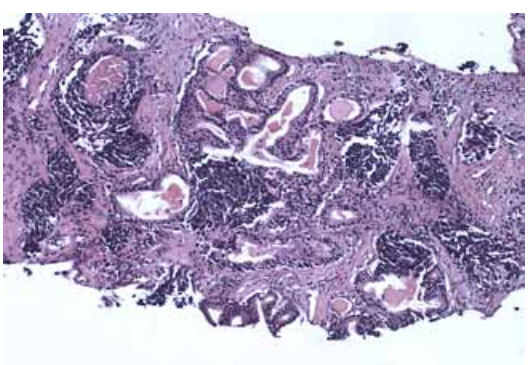

Figure 3 - *Small cell carcinoma in close association with Gleason 4+3 acinar adenocarcinoma (same case as Figure-4). Hematoxilin-eosin, 100x.*

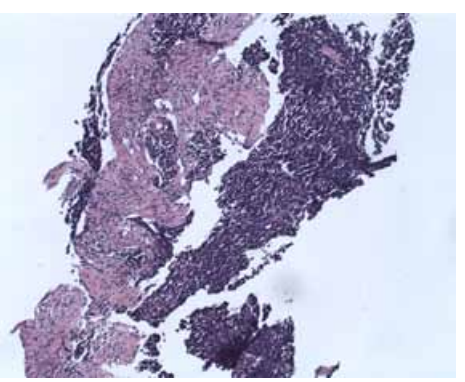

Figure 4 - *Medium-power view of small cell carcinoma. The tumor tends to fragment on processing. Hematoxilin-eosin, 100x.*

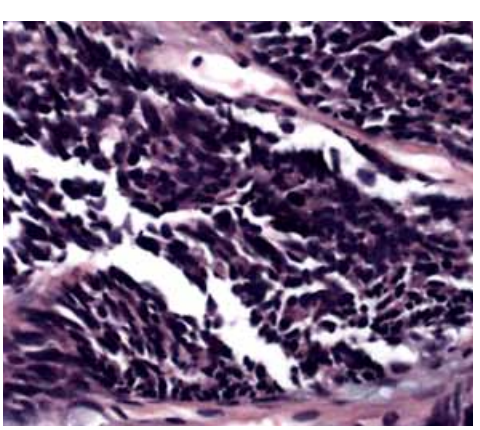

Figure 5 - *Small cell carcinoma. Punctuate tumor necrosis is a common finding. Also note the desmoplastic stroma surrounding tumor nests. Hematoxilin-eosin, 200x.*

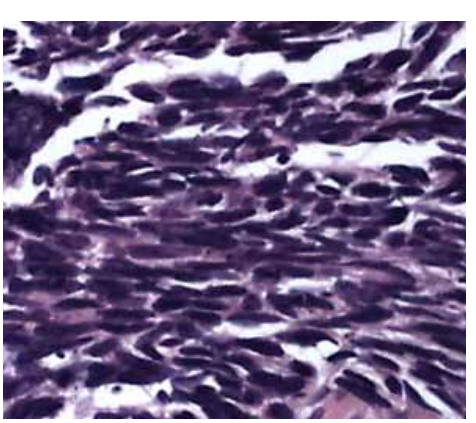

Figure 6 - *Small cell cacinoma, cytologic findings. Small cell carcinoma. Nucleoli are inconspicuous and cytoplasm are scant. Hematoxilin-eosin, 200x.*

Table 1 *- Pathologic characteristics of neuroendocrine carcinomas.*

Case	Age	Associated acinar adenocarcinoma	Gleason score of associated adenocarcinoma	Number of cores involved by NEC	Mean percent of involved cores	PSA IHC score in NEC component	Chromogranin	Synaptophysin	Ki-67	Necrosis (%)	Mitoses/10HPF
1	70	yes	9	10/12	60	2	3	3	60	20	7
2	79	yes	8	8/8	90	0	3	2	90	0	19
3	66	no	NA	2/8	20	0	2	2	40	0	14
4	75	no	NA	7/8	75	0	3	2	60	5	6
5	76	yes	7	2/6	35	NA	2	2	NA	0	12
6	49	no	NA	3/6	30	1	3	3	75	0	12
7	70	No	NA	4/8	20	2	2	1	NA	45	28

Table 2 *- Clinical and follow-up characteristics of neuroendocrine carcinomas.*

Case	Surgery	QT	HT	Status at follow-up	PSA at diagnosis	Clinical stage	Follow-up time (month)
1	No	Yes	No	DOD	7.33	T4N0M1c	8.1
2	TUR/orchiectomy	Yes	Orchiectomy	LWD	285.0	T4N0M0	21.3
3	no	No	No	LFU	NA	NA	NA
4	no	Yes	No	LWD	103.3	T4N1M1b	26.6
5	no	No	Yes	LWD	1449.0	T4N0M1b	22.2
6	Palliative colostomy	No	No	DOD	NA	T4N1Mx	2.1
7	TUR	No	No	DOD	0.04	T3NxM1b	2.1

five available cases. PSA immunohistochemistry was only weakly positive in NEC in 2 cases (Figures 7-10).

During the same period, data on 458 conventional type acinar adenocarcinomas were reviewed and compared with the seven cases on this study. Of the 458 cases, there were 191 Gleason 6, 131 Gleason 7, 72 Gleason 8, 33 Gleason 9 and 7 Gleason 10. The mean age at diagnosis correspondent to Gleason 6-10 were 69.1, 70.3, 74.2, 73.6 and 76.2 ($p < 0.001$). Within the acinar tumors, high grade tumors (Gleason > 7) also correlated with a high PSA at diagnosis ($p < 0.001$), but not with prostate volume ($p = 0.3$). The ratio of PSA/volume significantly correlated with a high Gleason score ($p < 0.05$).

The number of cores involved in prostates with NEC was greater (65% compared to 24% of acinar tumors, $p < 0.05$). The mean PSA at diagnosis was 417.7 (range 5.7-1593, SD 218.3), compared to 100.5 ($p = 0.1$) of acinar tumors (range 0.3-8545, SD 22.7). Prostates harboring NEC were bigger ($p < 0.001$, mean volume 240 mL vs 53 mL of acinar tumors).

Follow-up was available in six patients. Treatment of our patients included chemotherapy and hormonal therapy, as well as palliative surgery. Most patients were diagnosed in an advanced stage, precluding the possibility of radical prostatectomy. Three patients underwent palliative surgery: one was treated with transurethral resection only for obstruction, a second with transurethral resection followed by surgical castration (orchiectomy) and a third with colostomy for intestinal obstruction by metastatic tumor. Three patients were treated with chemotherapy in association with etoposide phosphate (VP-16) and cisplatin (CDDP). In one of these patients, chemotherapy was suspended after one cycle due to obstructive renal failure, whereas in another patient the regimen was modified to taxol after the fourth cycle, but with no measurable response. Mean follow-up was 13.7 months, with a range of 2.1 months in two patients with distant metastatic disease at diagnosis (bone in one, and bone and liver in the second), to 26.6 months in a patients who is alive with disease at last follow-up (Table-2).

DISCUSSION

The morphologic features of NEC of the prostate are similar to those of other sites, including the common pulmonary small cell carcinomas (9). In prostate neuroendocrine carcinoma series, however, a common finding is the association with conventional acinar tumors, suggesting a common pathway of tumor differentiation, or a neuroendocrine transformation from the better-differentiated carcinoma to neuroendocrine tumor (7,11). In the current study, only of the cases showed associated conventional type cancer; however, it is noteworthy that these were all diagnosed on needle biopsies, and one can not exclude another tumor components if the tumors were resected and examined throughout.

The diagnosis of high-grade neuroendocrine carcinomas in a needle biopsy may be challenging to the pathologists, especially because of the important clinical implication, which is exclusion from tentative surgical treatment with curative intent. None of the patients in the series were taken to radical prostatectomy, with two patients undergoing transurethral resection for obstructive disease palliative management. This data underscores the need for new therapeutic strategies to treat these tumors, which may include the use of protocols that have been effective against neuroendocrine carcinomas arising in other organ systems (6,12-14).

In cases where the diagnosis of small cell carcinoma is difficult, either due to the limited materials available, or due to lack of clear neuroendocrine differentiation, where the main differential is always with high-grade Gleason 9 or 10 acinar prostate adenocarcinomas, and poorly differentiated urothelial tumors invading the prostate, immunohistochemistry can be helpful. The vast majority of these tumors express at least one neuroendocrine marker. Wang et al. reported a rate of 94%, being CD56 the most sensitive (7). One caveat is that conventional adenocarcinomas, up to 100% in some studies, may focally express these same markers, reinforcing the need for careful morphologic evaluation by the pathologist (5,15,16). More recent discoveries have suggested that prostatic specific membrane antigen (PSMA), CD44 and

protein (P501S) may help with indentifying neuroendocrine expression in tumors (7,17).

High-grade neuroendocrine carcinomas have been reported in association with obstructive symptoms in the setting of androgen-independent disease. In this scenario, serum PSA levels tend to be low to undetectable. In the current series, all cases were diagnosed de novo with a high mean PSA, indicating that those tumors or the associated acinar tumor are able to express high quantities of PSA. Interestingly, we have found no association of serum PSA levels and PSA detection on the tissue by immunohistochemistry (Tables 1 and 2).

CONCLUSIONS

Prostates harboring neuroendocrine carcinoma tend to be larger and involve a greater number of cores than acinar tumors. Association with conventional acinar tumors is common. Serum PSA levels vary greatly and its value at diagnosis does not seem to predict the presence of NE tumors in needle biopsy.

CONFLICT OF INTEREST

None declared.

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Bladder exstrophy: reconstructed female patients achieving normal pregnancy and delivering normal babies

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ABSTRACT

Purpose: Bladder exstrophy (BE) is an anterior midline defect that causes a series of genitourinary and muscular malformations, which demands surgical intervention for correction. Women with BE are fertile and able to have children without this disease. The purpose of this study is to assess the sexual function and quality of life of women treated for BE.
Materials and Methods: All patients in our institution treated for BE from 1987 to 2007 were recruited to answer a questionnaire about their quality of life and pregnancies.
Results: Fourteen women were submitted to surgical treatment for BE and had 22 pregnancies during the studied period. From those, 17 pregnancies (77.2%) resulted in healthy babies, while four patients (18.1%) had a spontaneous abortion due to genital prolapse, and there was one case (4.7%) of death due to a pneumopathy one week after delivery. There was also one case (5.8%) of premature birth without greater repercussions. During pregnancy, three patients (21.4%) had urinary tract infections and one patient (7.14%) presented urinary retention. After delivery, three patients (21.4%) presented temporary urinary incontinence; one patient (7.14%) had a vesicocutaneous fistula and seven patients (50%) had genital prolapsed. All patients confirmed to have achieved urinary continence, a regular sexual life and normal pregnancies. All patients got married and pregnant older than the general population.
Conclusions: BE is a severe condition that demands medical and family assistance. Nevertheless, it is possible for the bearers of this condition to have a satisfactory and productive lifestyle.

Key words: *bladder exstrophy; outcomes; female; pregnancy*
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INTRODUCTION

Bladder exstrophy (BE) is an anterior midline defect with variable expression involving the infraumbilical abdominal wall including the pelvis, urinary tract, and external genitalia resulting in the exposure of the distal urinary tract to the outer abdominal wall (1). Its incidence varies from 1:30,000-1:50,000 live births, being up to 2.8 times more frequent in the male sex and 1.7 times more frequent in caucasians (2-4). There is a risk of recurrence of 0.5-3.0% in families with one affected subject. This value represents a small risk of recurrence, but it is as high as 200- to 800-fold when compared with the unaffected population (1). No etiological genetic or non-genetic factor has been identified so far; however some chromosomal candidate regions causally related to bladder exstrophy are starting to be identified (5).

The approach of patients with BE is an enormous challenge in Pediatric Urology. Besides the satisfactory closure of the abdominal wall the

treatment must also aim for kidney preservation, urinary continence, and avoidance of complications (6). The treatment for BE consists of two basic options: staged reconstruction and complete primary repair. The staged reconstruction of BE consists of initially closing the bladder plate and posterior urethra, with subsequent steps of epispadia repair and finally bladder neck reconstruction. The complete primary repair involves the closure of the bladder plate and urinary tract reconstruction through colocystoplasty or ureterosigmoidostomy (6). Epispadia repair is also done in the same surgical procedure.

The quality of life of individuals with BE is considerably affected by the disease. Children and adolescents present a high level of school education, social integration and even an active sexual life (7). Several studies demonstrated a good satisfaction level with aesthetical results of surgery, but still many patients are not satisfied with their physical appearance, especially with their genitals, avoiding body exposure situations (7-9). Adult women's quality of life has also been assessed, showing satisfactory results regarding social, professional, and sexual life. Nevertheless, urinary incontinence, genital prolapse and psychological distress are present in many cases (10).

Women treated for BE are capable of having normal children. These pregnancies require a great demand of attention from the physicians since they are complex cases (10). The purpose of this is study is to evaluate the sexual function, quality of life and pregnancies from the female patients treat for BE in our institution.

MATERIALS AND METHODS

The patient charts of all patients treated for BE from 1987 to 2007 in our institution were reviewed, totaling 30 charts. Those patients were called by telephone and invited to participate the study. The participating patients were interviewed by phone by the performers of this study about the age they had their first pregnancy; the method of delivery; their children's current ages; whether they had an abortion; and whether any of their children have died and by which cause. They were also asked about any post-delivery complications, whether they had any kind of urinary leakage, and if they were sexually active. The patients' charts were also reviewed to determine to what kind of reconstruction the patients were submitted.

RESULTS

There were found to be 24 female patients, aged 18 or older, treated for BE in our institution, and 14 of them were successfully contacted and agreed to participate in the study. These 14 patients achieved 22 pregnancies, delivering 17 normal children (thirteen males and four females). The age of delivery of the first child varied from 20 to 32 years old (mean = 25.5 years). All babies were delivered through Cesarean section, with the exception of one that had a premature normal birth. The children's ages in 2007 varied from 1.5 to 11 years old (mean = 4.9 years). One child died one week after delivery due to a pneumopathy. There were also four spontaneous abortions related to genital prolapse.

Regarding urinary tract reconstruction, four patients were submitted to staged reconstructions for urinary tract reconstruction, another five were submitted to colocystoplasty for the repairment of BE, and the remaining five patients were submitted to ureterosigmoidostomies. All patients had pelvic posterior osteotomies on the reconstruction.

All the patients referred to urinary continence, which was translated as no need for pads, with mild to moderate eventual stress-related leakages. They were all sexually active and achieved normal natural pregnancies. All of them have stable marital lives and six (42.8%) have formal jobs.

Regarding pregnancy complications (Figure-1), there were the already mentioned four cases of abortions (18.1%), three patients (21.4%) presented urinary infections, one patient (7.14%) presented urinary retention, treated with clean intermittent catheterization, one child (7.14%) had a premature, normal birth and had a good recovery. After delivery (Figure-2) there were three cases (21.4%) of temporary urinary incontinence which had spontaneous improvement within 1 year after delivery, one case (7.14%) of vesicocutaneous fistula that demanded surgical correction, and seven patients (50%) had genital prolapse, including one who had to be submitted to a hysterectomy for this condition. The

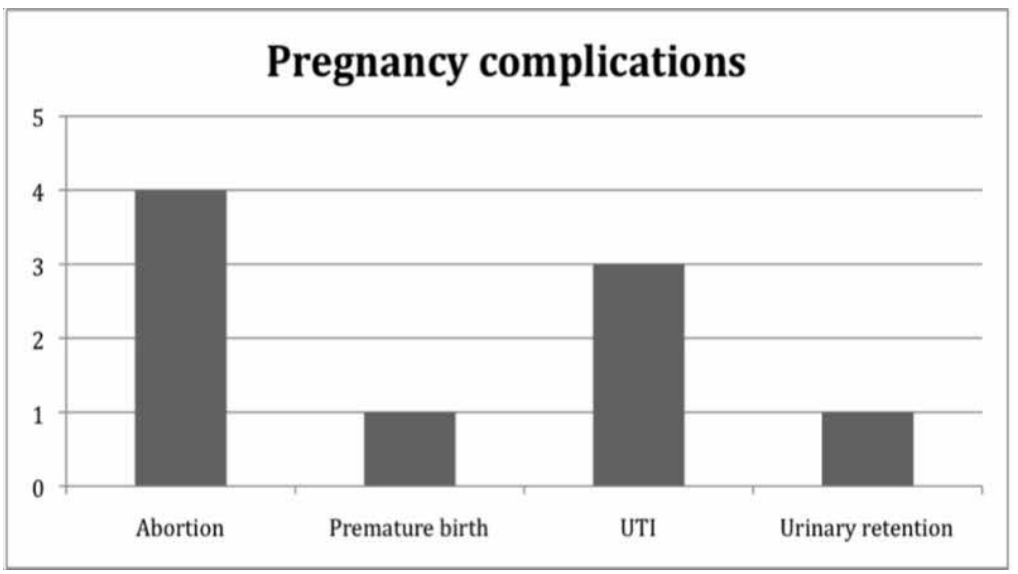

Figure 1 - *Pregnancy complications regarding the 22 pregnancies assessed.*

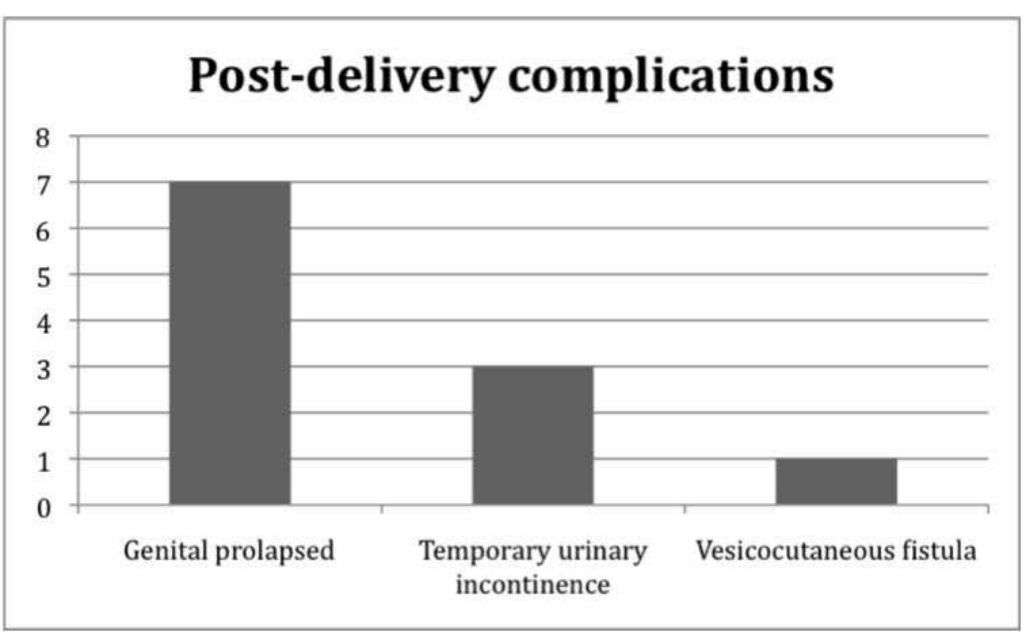

Figure 2 - *Post-delivery complications of the 14 patients. One of the genital prolapsed patients had to underwent a hysterectomy.*

other six patients had mild to moderate prolapse and were not submitted to surgical correction.

DISCUSSION

Bladder exstrophy has a major impact in the life of patients affected by the disease and their families. Parents of children suffering from BE experience more stressors than the average population (e.g. worrying about the long-term impact of the illness, helping the child with his/her hygiene needs), and when facing increased stress they sometimes cope through avoidance and distancing, harming the child and the familiar structure itself (11). Observing the challenges BE inflicts, it is not surprising that suicidal ideation is also a frequent issue families, patients and physicians have to cope with. A study with 121 patients showed that almost 15% experienced suicidal ideation, with an increase in this number to 38%, when only those aged 14 years and older are considered, including two cases of suicide attempt and one case of suicide (12).

Besides the social and psychological implications of BE there are also several other repercussions of the disease, including the ones from the corrective surgeries and from the associated morbidities of the disease even when treated. Some complications of any method of primary bladder exstrophy closure are complete wound dehiscence, bladder prolapsed, urethral outlet obstruction, bladder calculi, pubic separation, renal calculi and corporal loss; other rarer complications include osteotomy non-union, leg length inequality, persistent joint pain, posterior bladder outlet obstruction, urethrocutaneous fistula, urinary infection, and surgical site infection (13-14). In addition, patients with BE have a 694-fold increase in the risk of bladder cancer by the age of 40, with a higher incidence of cystitis glandularis, which is related to the genesis of adenocarcinomas, demanding intense surveillance of these patients when they achieve adulthood through urine cytology and cystoscopy (15,16). Furthermore, with the optimized treatment options, patients with BE are living longer and the first case of prostate cancer has already been reported, demonstrating the need for screening in these patients, as they get older (17).

Our study presents an abortion rate of 18.1%, against a 12.4% rate of a major pregnancy morbidity study (n = 24.481) (18). Moreover, we present a urinary infection rate of 21.4%, compared with a 5.0% rate of the same mentioned study (18). Regarding temporary urinary incontinence, its incidence can be as high as 80% in some moment of the pregnancy, keeping rates around 20% shortly after delivery, which is comparable to our 21% rate of incontinence after delivery (19). A similar study targeting pregnancy after lower urinary tract reconstructions demonstrated similar findings, with 27 women and 34 pregnancies having the following complications: an injury to the vascular pedicle of the cystoplasty without sequelae and six cases (17.6%) of temporary urinary incontinence (20). Urinary retention and vesicocutaneous fistulas are rare occurrences during pregnancies (21,22).

We found a higher incidence of genital prolapsed in our casuistic when compared with the literature, with 50.0% of our patients with genital prolapsed against a median frequency of 30.0% in the literature, we had one severe case of genital prolapsed which culminated into a hysterectomy, but the other six cases had mild to moderate prolapses, which are being followed since there are no complaints of major discomfort for this condition (10). Female patients with BE are expected to have some degree of vaginal prolapse, especially after a second pregnancy, even without vaginal delivery. Some authors suggest that bed rest for the pregnant mother during the third trimester may diminish this complication (23). Elective Cesarean section is the most recommended delivery for protecting continence and avoiding prolapses (24).

All of our patients were sexually active and had stable marital lives. A study assessing the quality of life of women born with BE presented a stable relationship rate of 64% and sexual activity in 76% (10). A high percentage of women were actively working (59%) against 42.8% of our series, but persistent urinary incontinence was present in 65% of their patients and in none of ours (10). Other studies assessing continent urinary diversion found continence rates of less than 15%, more similar to our findings (25).

CONCLUSIONS

Patients with BE may have a satisfactory and productive lifestyle. They can get married and have children, but they should take extra care during pregnancy and after delivery for they may have more complications than people without this condition.

CONFLICT OF INTEREST

None declared.

ABBREVIATIONS

BE - Bladder Exstrophy

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Alkaline citrate reduces stone recurrence and regrowth after shockwave lithotripsy and percutaneous nephrolithotomy

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ABSTRACT

Objective: To evaluate the preventive effects of alkaline citrate on stone recurrence as well as stone growth post-ESWL or PCNL in patients with calcium-containing stones.
Materials and Methods: A total of 76 patients with calcium calculi who were stone-free or had residual stones less than 4 mm following ESWL and PCNL were enrolled. All patients were independently randomized into two groups. The treated group (N = 39) was given 81 mEq per day of oral potassium-sodium citrate (27 mEq three times a day), and the untreated group (N = 37) serving as controls. Blood, twenty-four hour urine analysis, and plain KUB were measured and compared at the baseline and after 12 months.
Results: At baseline, hypocitraturia was found in 20 of 39 patients (46.05%) of Group I and 15 of 37 patients (40.5%) of Group II. At 12 months, hypocitraturia was found in 3 of 39 (7.69%) and 14 of 37 (37.83%) of Group I and Group II, respectively (p = 0.007). At the 12 month follow-up, of the stone-free group, 92.3% of the treated group and 57.7% of the control group were still stone free. Of the residual stone group, 30.8% and 9.1 % of treated and control group were stone-free, respectively. The increased stone size found in 7.7% and 54.5% of treated and control groups, respectively.
Conclusion: Sodium-potassium citrate provides positive effects on stone-forming activities in calcium stone patients suffering from urolithiasis following treatment with ESWL and PCNL procedures at the 12-month follow-up.

Key words: *kidney; calculi; lithotripsy; citrates; urolithiasis*
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INTRODUCTION

With the advantage of high efficiency and low morbidity rates, extracorporeal shock wave lithotripsy (ESWL) has become the therapy of choice for small renal stones. Percutaneous nephrolithotomy (PCNL) is also becoming the therapy of choice for large renal stones due to the less invasive procedure as compared to open nephrolithotomy. These therapies provide good results, associated with an acceptable rate of complications, but unfortunately they do not change the underlying metabolic abnormality. Stone recurrence is usually found after either treatment, even in those with a stone-free post-therapy status. In addition, retained stone fragments following those therapies may reaggregate or constitute a nucleus for new stone formation, thereby causing a high rate of stone growth (1-4). The patient's chances of first episode recurrent stone formation range between 27% and 50% (5,6). Medical treatment should therefore be considered following these interventions, in order to prevent further secondary treatments and hospitalizations. Among the metabolic disorders usually found in recurrent stone forming patients, hypocitraturia

(low urinary citrate) is an important risk factor for calcium nephrolithiasis (1-4). Several studies demonstrated the effect of alkaline citrate in prevention and/or reduction of the stone recurrence and stone growth (1-4). In the current study, we evaluated the preventive effects of potassium-sodium citrate on stone recurrence as well as stone growth post-ESWL or PCNL, in patients with calcium-containing stones.

MATERIALS AND METHODS

The study was approved by the ethics committee of the Faculty of Medicine, Chiang Mai University. Patients gave written informed consent before participating in the study.

Eighty patients, who were stone-free or had residual stone fragments with less than 4 mm diameter at eight weeks after ESWL or PCNL, were enrolled in the present clinical study. In case of ESWL, patients were treated by using Storz™ Modulith SL-20 equipment; in case of PCNL a standard nephroscopy (26-Fr Storz™ nephroscope) under fluoroscopic guidance with combined ultrasound and pneumatic lithotripsy was performed. All patients had calcium stones after the analysis by infrared spectrometry method. Four patients were excluded from the study due to loss of follow-up (N = 3) and unsatisfactory compliance with medication (N = 1). In total, 76 patients completed the one-year follow-up period. Eight weeks after the ESWL/PCNL therapies, plain KUB films were evaluated: 39 patients were stone-free (ESWL n = 24, PCNL n = 15) and 37 had residual stones smaller than 4 mm in diameter (ESWL n = 26, PCNL n = 11).

All patients were independently block randomized into two groups: the treated group and the untreated group. The treated group (n = 39) was given 81 mEq oral potassium-sodium citrate (Uralyt-U®, Rottapharm Madaus) per day (27 mEq three time a day), whereas the control group (n = 37) received no treatment. All patients had normal renal function and normal renal anatomy, as assessed by preoperative intravenous pyelography study. All patients who had urinary tract infections, anatomic abnormalities and clinical history of urologic stone surgery were excluded.

At baseline, all patients were evaluated for blood urea nitrogen (BUN) creatinine, electrolytes, complete blood count (CBC), calcium, uric acid, urinalysis; in the 24-hour urine study, total urine volume, creatinine, electrolyte, calcium, oxalate, Uric acid?

Uric acid and citrate were also measured. Patients were advised to have sufficiently high fluid intake throughout the study, and the follow-up was scheduled every 3 months.

The patients were reevaluated at six months after the initial treatment for serum chemistry and urinalysis. After 12 months, all patients were evaluated for serum chemistry, urinalysis, 24-hour urine study and plain KUB. The evidence of new stone formation was determined by spontaneous stone passage in absence of preexisting stones and/or appearance of new stones on a plain KUB film. Growth of existing stones was determined by quantification of increased stone size.

The statistical analyses were carried out using SPSS statistics software. Mann-Whitney U tests were used to compare laboratory tests, remission rates, and growth rates between groups. The difference within each group between baseline and 12 months post treatment was assessed by repeated measurement ANOVA and multivariate analysis.

The protocol and documents needed for this study have been reviewed and approved by the Ethics Committees of each participating hospital.

RESULTS

Of 80 patients recruited, 76 patients completed the 12-month follow-up observation period. The average ages were 51.7 ± 10.4 and 48.9 ± 10.7 years for the treated and control groups, respectively (Table-1). The average BMI was 23.9 ± 3.7 (kg/m^2) in treated group and 23.6 ± 3.2 (kg/m^2) in control group. The untreated group consisted of 25 patients (67.6%) post-ESWL and 12 patients (32.4%) post- PCNL. The treated group consisted of 25 patients (64.1%) post-ESWL and 14 patients (35.9%) post-PCNL. The average stone size in CIRF patients was 2.54 mm and 2.65 mm in treated and untreated patients, respectively. Laboratory tests such as complete blood count (CBC), blood urea nitrogen (BUN), creatinine, calcium, uric acid and sodium, chloride and bicarbonate did not show any significant difference at 6 months and 12 months as

Table 1 - *Profiles of patients at baseline.*

	Stone free		Residual Fragment < 4 mm	
	Citrate (N = 13)	**Control (N = 26)**	**Citrate (N = 26)**	**Control (N = 11)**
Sex				
Male	7 (53.8%)	17 (65.4%)	19 (73.1%)	9 (81.8%)
Female	6 (46.2%)	9 (34.6%)	7 (26.9%)	2 (18.2%)
Age (year)	48.8 ± 8.26 (35 - 64)	54.1 ± 10.12 (32 - 73)	49.1 ± 12.04 (28 - 75)	45.9 ± 8.93 (31 - 57)
Post treatment				
ESWL	8 (61.5%)	16 (61.5%)	17 (65.4%)	9 (81.8%)
PCNL	5 (38.5%)	10 (38.5%)	9 (34.6%)	2 (18.2%)

compared with the baseline values, in both groups. Only a significant increase of serum potassium, albeit well within the physiological range, was found in the treated group at 12 months (from 4.02 ± 0.42 to 4.29 ± 0.48 mEq/L, p = 0.011). Urine pH and urine potassium were significantly increased from baseline at 6 months and 12 months (p = 0.001 at 6 month, p = 0.09 at 12 month). The level of urine potassium in treated patient was significant increased from 27.7 ± 18.3 to 56.7 ± 25.4 at 6 months and to 49.5 ± 36.4 at 12 months. At baseline, the result of 24-hour urine measurement for total urine volume, sodium, potassium, chloride, creatinine, calcium, magnesium, oxalate uric acid, and citrate did not show significant difference between both groups (Table-2). The average values of citrate were 304.3 ± 233.8 mg/d and 259.2 ± 214.7 mg/d in control and in treated group, respectively. Hypocitraturia, with citrate values lower than 320 mg/day was found in 35 out of the total 76 patients which was 46.05% of total patients, 15 patients in control group (92.9 ± 64.96 mg/day) and 20 in treated group (169.5 ± 98.4 mg/day). Mean urine citrate level at month 12 was 305. 3 ± 233.08 mg/day in control group and 405.3 ± 305.44 mg/day in treated group which is statistically significant (P = 0.007). Low urine output (urine volume lower than 1,500 ml/d) was a common secondary finding observed in 40.8% of all patients. Number of patients in both groups who have abnormal 24-hour urine measurement was shown in Table-2.

The change of the stone, assessed at 12 months follow up, is shown in Table-3. In the stone-free group at baseline, 92.3% of treated group and 57.7% of control group were still stone free at 12 months. An increase in stone size was found in 7.7% and 42.3% of treated and control group, respectively, which were statistically different. At the same 12-month follow-up, in the group with residual stone fragments < 4 mm in diameter, 30.8% and 9.1% of patients were found to be stone-free in the treated and control groups, respectively. 50% of patients in the treated group showed the same stone size, whereas an increase in stone size was found in 7.7% and 54.5% of the treated and control groups, respectively.

DISCUSSION

The most common composition of kidney stones is calcium-based, which is up to 80% of all types of stones (7). The purposes of stone management are complete stone clearance, prevention of new stone formation and regrowth, preservation of renal function, control of urinary tract infections and, whenever the case, correction of abnormal anatomy and underlying metabolic abnormality. The advancement in minimally invasive surgery, most kidney stones are treated with extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy (PCNL). Following these treatments, the achievement of stone-free condition or of residual fragments with a diameter smaller than 4 mm is de-

Table 2 *- 24 hours urine metabolic evaluation.*

Urine 24 hours	Citrate (N = 39)	Control (N = 37)	P-value
Total volume (< 1500 mL/day)			
Month 0	17 (43.6%)	14 (37.8%)	
Month 12	15(38.5%)	20 (54.1%)	0.331
Hypercalciuria (>300 mg/d,♂; > 250 mg/d,♀)			
Month 0	4 (10.3%)	7 (18.9%)	
Month 12	8 (20.5%)	7 (18.9%)	0.391
Hyperoxaluria (> 40 mg/d)			
Month 0	8 (20.5%)	6 (16.2%)	
Month 12	8 (20.5%)	10 (27.0%)	0.476
Hyperuricouria (> 600 mg/d)			
Month 0	1 (2.6%)	0	
Month 12	1 (2.6%)	3 (8.1%)	0.171
Hypocitraturia (< 320 mg/d)			
Month 0	20 (51.3%)	15 (40.5%)	
Month 12	3 (7.69%)	14 (37.83%)	0.007
Urine pH			
Month 0	5.8 ± 0.77	5.7 ± 0.66	
Month 12	6.6 ± 0.97 (P = 0.001)	5.9 ± 0.70 (P = 0.09)	

Table 3 *- Stone-forming activity at 12 months (Overall n = 76).*

	Stone free(%)			Residual Fragment < 4 mm (%)		
	Citrate n = 13	**Control n = 26**	**RR (95% CI)**	**Citrate n = 26**	**Control n = 11**	**RR (95% CI)**
Stone free	12(92.3)	15(57.7)	5.33 (0.77 - 36.5)	8(30.8)	1(9.1)	1.38 (0.96 - 1.98)
Stone size unchanged	-	-		13(50.0)	2(18.2)	1.47 (0.98 - 2.18)
Stone size decreased	-	-		3(11.5)	2(18.2)	0.83 (0.39 - 1.76)
Stone recurrence / Stone size increased	1(7.7)	11(42.3)	0.19 (0.03 - 1.28)	2(7.7)	6(54.5)	0.30 (0.08 - 1.0)

fined as a therapeutical success (1,2). The presence of residual fragments is commonly found following these modern treatments, particularly after ESWL (1,2,8). It is clinically relevant, as a recognized predisposing factor for new stone formation (1-4), recurrent urinary tract infections, pain and, in general, for need of further additional treatments (1).

By analyzing stone-forming activity at two years following ESWL, it was found that the incidence of recurrent stones ranged from 8% to 10% in stone-free patients and from 20% to 22% in patients with residual fragments (8). Another study found recurrent calculi, in patients who had stone free status after ESWL, ranging from 7% to 14% per year (9). In comparing Soygur's and Fine's studies at 12 months after ESWL, the alkaline citrate-treated patients who were stone-free at baseline and remained stone-free were 100% and 89.5%, respectively. However, there were found to be only 71.4% and 50% in untreated patients of both studies respectively (2,10). Nine per-

cent of patients following PCNL had recurrent stones following achievement of stone-free condition, and 63% had either new calculi or continued stone growth after having residual stone fragments (3).

Metabolic abnormalities were also detected in the majority of patients with recurrent nephrolithiasis. The wide range of underlying metabolic abnormalities such as hypercalciuria, hyperoxaluria, hyperuricouria and hypocitraturia can cause the formation of stones in the urinary tract metabolic abnormalities were not affected following ESWL / PCNL therapies. Our common metabolic abnormalities are hypocitraturia followed by hypercalciuria and low urine output, which is the same as the previous study from Thailand (11). Effective medical management should therefore be directed primarily towards correction of the underlying abnormalities. As expected, stone-free status and residual fragments status following ESWL and PCNL still increased the risk for active stone formation (1,2,10). Such medical treatment significantly alleviated stone-forming activity after ESWL and PCNL in patients who resulted stone-free as well as those with residual fragments (1,2,10). The remission rate of patients with residual calculi was significantly lower than the stone-free group (1-4).

Citrate is the most potent stone inhibitor (12,13). The mean normal urinary citrate excretion is 640 mg/24 hours of urine. The accepted limit for diagnosing hypocitraturia is 320 mg/24 hours of urine (2). Isolated hypocitraturia has been identified in about 13% of patients, and coexists with other metabolic abnormalities in 15% to 69 % of calcium stone formers (7,11). Hypocitraturia is usually found in patients with systemic acidosis, hypokalemia, unbalanced diets, and chronic diarrhea. The mechanism of action of citrate in the prevention of calcium urolithiasis relates to its ability to form a complex with calcium in urine as calcium citrate complex, which is more soluble than calcium oxalate (7,12,13). The calcium citrate complex prevents all forms of crystallization by inhibiting spontaneous nucleation of calcium oxalate and/or crystal growth of calcium phosphate and calcium oxalate, by retarding agglomeration of preformed calcium oxalate crystal, and by preventing heterogeneous nucleation of calcium oxalate; monosodium urate citrate also restores the inhibitory properties of Tamn-Horsfall protein (7).

Several authors supported the benefit of alkaline citrates in all patients undergoing shock-wave lithotripsy for the significant improvement in rates of alleviation the calcium oxalate stone-forming activity and positively influence the preexisting stone clearance and dissolution with minor adverse reaction (2,11,14-16). The studies with stone recurrence as the endpoint demonstrated a reduction in stone-forming rate from 47% to 100%. Of four randomized controlled trials, the stone-free rate after at least two years of alkaline citrate treatment was 53.5% and 35% in treatment and placebo groups, respectively (3,14-16). For three years, in idiopathic hypocitraturic calcium nephrolithiasis patients who received potassium citrate, the stone formation per year significantly declined from 1.20.6 to 0.1 ± 0.2 stones per patient. This positive effect of potassium citrate also found in calcium stone patients following PCNL (3). Authors concluded that the medical therapy can decrease costs of repeated procedures and recommended it for patients following PCNL regardless of their stone-free status. After potassium citrate, minor gastrointestinal side effects such as diarrhea, indigestion, nausea and burning may occur.

Our study demonstrated that hypocitraturia (urine citrate excretion < 320 mg/24-hours urine) was the most common metabolic risk factor in our patients after ESWL and PCNL. We have found that in these kinds of patients, the medical therapy with potassium-sodium citrate can prevent and/or reduce the recurrence and stone growth during a 12-month follow-up. The patients with residual fragment < 4 mm post-treatment were at risk for developing stone growth, as demonstrated in control group compared with the treated group. Our study showed that stone-free status and unchanged stone size status were significantly more frequent in the treated group which is 5.3 fold in stone-free patients and 1.38 fold in CIRF patients as compared to the untreated group. Moreover, the oral formulation of potassium-sodium citrate was well-tolerated with significantly less reported side effects. During the follow-up time, only an increase of serum potassium (but within the normal range), urine pH, and urine citrate were ob-

served as related with the therapeutic effects of the medication.

The limitations of this study are the small number size and short follow-up time. Due to the poor compliance with alkaline citrate treatment in stone patients with a long follow-up period in clinical practice, this study can demonstrate the positive effect of potassium-sodium citrate in one year follow-up.

CONCLUSIONS

Hypocitrauria is the most common metabolic disorder in calcium stone patients. Sodium-potassium citrate provides positive effects on stone-forming activities, in a 12- month follow-up in calcium stone patients. We therefore recommend administration of alkali citrates in patients suffering from urolithiasis, following treatment with ESWL and PCNL procedures, for effective prevention of stone recurrence and stone growth.

CONFLICT OF INTEREST

None declared.

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Inflammation and endothelial activation in Benign Prostatic Hyperplasia and Prostate Cancer

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ABSTRACT

Purpose: Emerging insights underline a link among chronic inflammation and endothelial activation with benign prostatic hyperplasia (BPH) and prostate cancer (PCa). We aim to investigate whether specific plasma markers of inflammation and endothelial activation allow to discriminate BPH and PCa.
Materials and Methods: Fifteen patients affected by BPH, 15 by PCa and 15 controls, were enrolled. Interleukin-6 (IL-6), CD40 ligand (CD40L), endothelial-selectin (E-selectin), platelet-selectin (P-selectin), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) were measured.
Results: In systemic blood samples, IL-6 has been found increased in patients affected by BPH (4.25 ± 0. pg/mL) and PCa (5.08 ± 0.24) respect to controls (2.62 ± 0.34; $p < 0.05$). CD40L was higher in BPH (4.25 ± 0.65 ng/mL; $p < 0.05$) than in control (2.31 ± 0.20) and PCa group (2.60 ± 0.56). E-selectin, P-selectin and VCAM-1 did not show any significant difference. Higher levels of ICAM-1 were detected in patients with PCa (573.04 ± 52.23) and BPH (564.40 ± 74.67) than in the controls (215.30 ± 11.53 ng/mL; $p < 0.05$). In local blood samples, IL-6 has been found significantly increased in PCa in comparison with patients with BPH; there was no difference in CD40L, E-selectin, P-selectin, VCAM-1 ed ICAM-1.
Conclusions: Changes in inflammation and endothelial activation markers may be not considered to be of value in discriminating BPH and PCa.

Key words: *prostatic hyperplasia; prostatic neoplasms; biological markers; inflammation mediators; endothelial cells*
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INTRODUCTION

The pathogenesis of PCa (prostate cancer) and BPH (benign prostatic hyperplasia) is still largely unresolved. The common key mechanisms involved in the development and progression of PCa and BPH are represented by ageing, hormonal alterations, metabolic syndrome and inflammation (1). Currently, a vast literature suggests a link between chronic inflammation and prostatic disease (2,3). However, whether intraprostatic inflammation may contribute to carcinogenesis and hypertrophy of prostate is still unknown. The molecular pathogenesis of prostate cancer has been characterized by somatic germline alterations of genes associated with some immunological aspects of inflammation in modulating prostate cancer risk. In support of this hypothesis, population studies pointed out an increased relative risk of prostate cancer in patients with a previous history of sexually transmitted infections or prostatitis (4-6). Proliferative inflammatory atrophy, which shares

some molecular traits with prostate intraepithelial neoplasia and prostate cancer, has been recognized as a novel putative prostate cancer precursor lesion (7). Nonetheless, inflammation is frequently present in prostate biopsies, radical prostatectomy specimens and tissue resected for the treatment of benign prostatic hyperplasia. Moreover, proliferative inflammatory atrophy, often found inside and around foci of atrophy, may be considered as a precursor of an early prostate cancer or may indicate an intraprostatic environment favourable to cancer development.

In the last few years, the role of inflammation in the pathogenesis of BPH has been also advocated in supporting the process of fibromuscolar growth (3-7). The inflammatory injury may contribute to cytokine production by inflammatory cells driving local growth factor production and angiogenesis in the prostatic tissue. An up-regulation of pro-inflammatory cytokines has been reported in BPH tissue (8). This pro-inflammatory micro-environment is closely related to BPH stromal hyperproliferation and tissue remodelling with a local hypoxia induced by increased oxygen demands by proliferating cells which supports chronic inflammation as a source of oxidative stress leading to tissue injury in infiltrating area (9). When taken together, studies of sexually transmitted infections, clinical prostatitis, genetic and circulating markers of inflammation hint at a link between prostate cancer and chronic intraprostatic inflammation (10). Analyses on bacterial colonization in PCa and normal prostate tissue showed, indeed, a highly suggestive correlation between bacterial colonization/chronic inflammation and PCa as well as BPH. The hypothesis that inflammation might promote PCa and BPH is actually supported by several new significant findings. On the basis of these suggestions, aim of this study has been to investigate the possible significance of markers related to inflammation and endothelial activation as discriminative indexes of PCa or BPH. For this purpose, we measured, in blood samples withdrawn both locally in the prostate gland and systemically, interleukin-6 (IL-6), CD40 ligand (CD40L), endothelial-selectin (E-selectin), platelet-selectin (P-selectin), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) as specific markers of inflammation and endothelial activation.

MATERIALS AND METHODS

A total of 45 consecutive patients, hospitalized in our Urological Department between February and July 2008, 15 affected by BPH, 15 by PCa and 15 controls were selected for the current study. The research has been carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of our hospital. Consent was obtained from all patients after full explanation of the procedure. Details about the criteria of selection and methodological procedures have been just described in a previous study (11).

In serum and plasma blood samples we measured: IL-6, CD40L, E-selectin, P-selectin, VCAM-1 and ICAM-1. Plasma and serum samples were stored at -80°C until analysis.

VCAM-1 and ICAM-1 levels (ng/mL) were measured using ELISA kits (Bender MedSystems GmbH, Campus Vienna Biocenter, Austria), with a sensitivity of 0.59 ng/mL and 2.17 ng/mL, an intra-assay CV of 3.1% and 4.1%, an inter-assay CV of 5.2% and 7.6%, respectively.

P-selectin and E-selectin levels (ng/mL) were measured using ELISA kits (Bender MedSystems GmbH, Campus Vienna Biocenter, Austria), with a sensitivity of 1.06 ng/mL and 0.30 ng/mL, an intra-assay CV of 2.4% and 5.4%, an inter-assay CV of 5.2% and 6.0%, respectively.

CD40L level (ng/mL) was measured using a high sensitivity ELISA kit (Bender MedSystems GmbH, Campus Vienna Biocenter, Austria) with a sensitivity of 0.005 ng/mL, an intra-assay CV of 5.5% and an inter-assay CV of 6.6%. IL-6 level (pg/mL) was measured using an ELISA kit (Bender MedSystems GmbH, Campus Vienna Biocenter, Austria), with a sensitivity of 0.92 pg/mL, an intra-assay CV of 3.4%, an inter-assay CV of 5.2%.

SPSS for Windows (version 10.0.7) computer package was used for statistical analysis. All data are given as mean ± standard error of the mean (SEM). Mann-Whitney rank sum test was used to compare differences between all patients enrolled and the control group. Wilcoxon matched-pairs signed rank test was used to compare differences between local and systemic samples. Statistical significance was accepted if $p < 0.05$.

RESULTS

As reported in Table-1, in systemic blood samples we found an increased level of IL-6 in patients affected by BPH (4.25 ± 0.36 pg/mL) and PCa (5.08 ± 0.24) in respect to controls (2.62 ± 0.34; $p < 0.05$). This raise was significantly greater in patients with PCa than in those affected by BPH. CD40L was increased in BPH group (4.25 ± 0.65 ng/mL; $p < 0.05$) respect to controls (2.31 ± 0.20). Notably, in PCa patients we observed an increased value of CD40L statistically significant versus control group but not in comparison with BPH patients. No significant differences were observed in E-selectin, P-selectin and VCAM-1 among the three groups. Higher levels of ICAM-1 were detected in patients with both PCa (573.04 ± 52.23) and BPH (564.40 ± 74.67) than in the control group (215.30 ± 11.53 ng/mL; $p < 0.05$). However, no statistical significant difference was found in ICAM-1 between PCa and BPH. In local blood samples, IL-6 has been found significantly increased in PCa (7.14 ± 0.47) in comparison with BPH patients (6.35 ± 0.94). No significant differences were detected in CD40L, E-selectin, P-selectin, VCAM-1 ed ICAM-1 (Table-2).

Table 1 *- Parameters measured in systemic blood samples.*

	Control	**PCa**	**BPH**
IL-6 (pg/mL)	2.62 ± 0.34	5.08 ± 0.24*	4.25 ± 0.36* **
CD40L (ng/mL)	2.31 ± 0.20	2.60 ± 0.56	4.25 ± 0.65* **
E selectin (ng/mL)	54.67 ± 1.01	38.65 ± 5.23*	39.88 ± 8.20*
P selectin (ng/mL)	125.58 ± 0.84	45.71 ± 6.45*	37.94 ± 4.31*
VCAM-1 (ng/mL)	809.96 ± 26.48	333.65 ± 33.54*	361.97 ± 32.68*
ICAM-1(ng/mL)	215.30 ± 11.53	573.04 ± 52.23*	564.40 ± 74.67*

** P < 0.05 vs Control values; ** P < 0.05 vs PCa values; PCa: prostate cancer; BPH: benign prostatic hyperplasia.*

Table 2 *- Parameters measured in local blood samples.*

	PCa	**BPH**
IL-6 (pg/mL)	7.14 ± 0.47	6.35 ± 0.94*
CD40L (ng/mL)	1.99 ± 0.54	3.16 ± 0.76
E selectin (ng/mL)	34.32 ± 5.43	29.62 ± 4.25
P selectin (ng/mL)	177.80 ± 39.74	73.52 ± 12.63
VCAM-1 (ng/mL)	411.15 ± 68.80	383.53 ± 98.29
ICAM-1(ng/mL)	496.17 ± 36.49	466.04 ± 52.73

** P < 0.05 vs PCa values; PCa: prostate cancer; BPH: benign prostatic hyperplasia*

DISCUSSION

The identification of biomarkers, assessable in blood samples, in patients affected by PCa and BPH could be useful in order to differentiate those common prostate diseases as well as to identify specific therapeutic strategies. Patterns of inflammation and endothelial activation seem to offer a biological link between pathogenesis and clinical symptoms of prostatic disease as well as might predict the onset and progression of both PCa and BPH. Several studies support a close relation between BPH and the inflammatory pattern, as suggested by the increased rate (61%) of signs of chronic inflammation in prostates of greater volume (80-89 mL) respect to small ones (12). As prostate size is a valuable predictor of BPH progression, the relationship between prostate size and chronic inflammation should be indicative of worsening clinical development. Clinical evidence reports that chronic inflammation represents a key condition leading to prostate enlargement and to an increased symptoms score as well as a major risk of complications (3). Furthermore, when inflammation is clinically supposed and then proven histologically, it may be taken into account in the management and treatment of BPH. IL-6 is a pleiotropic cytokine and one of the main mediators of the acute phase reaction, produced by fibroblasts, activated macrophages or monocytes, activated T and B cells, endothelial cells, stromal cells (9). Besides, dysregulation of the immune response in BPH may occur via elevated expression of pro-inflammatory IL-17 which stimulates, in turn, IL-6 and-8 production responsible for stromal growth factor (3). According to these suggestions, we found IL-6 to be increased systemically in BPH respect to control group. This result confirms the involvement of IL-6 in the onset of BPH and could suggest its possible significance in discriminating prostate inflammatory hypertrophy in comparison normal gland tissue. A central role of the endothelial activation is also supported in the onset and progression of BPH by systemically increased levels of both CD40L and ICAM-1. It is well known that CD40/CD40L is involved in angiogenesis. Notably, CD40, demonstrated to be higher in advanced lung cancer, is also secreted by neoplastic prostatic epithelial cells by acting as a growth factor (13). In prostatic tumoral glandular tissue, CD40 is secreted with a higher rate in hormone-refractory phase, with a relevant importance in PCa progression (14). Tumorogenesis and progression are characterized by changed expression of cell adhesion molecules that are over-expressed in progressive disease and metastasis. However, current evidence underlines that expression of cell adhesion molecules may be not useful, over PSA, in differentiating PCa from BPH as well as for PCa diagnosis and follow-up (15). Moreover, E-selectin has been demonstrated to be constitutively expressed on bone marrow endothelial cells which represents the preferentially adhesive mechanism promoting haematogenous dissemination of prostate tumor cells into bone. Therefore, the acquisition of E-selectin ligand expression may be associated with prostate tumor progression (16). As showed by Shariat et al., increased plasma levels of IL-6, soluble IL-6 receptor, vascular endothelial growth factor, VCAM-1, endoglin, urokinase-type plasminogen activator and its receptor, plasminogen activator inhibitor-1, may be of value in predicting the risk of disease relapse after RP in respect to standard clinical variables, by 15% to 86.6% (17). E-selectin, expressed as a consequence of a hypoxic vascular condition, is up-regulated in PCa as result of complex interactions of tumor microenvironment and it is associated with tumor angiogenesis and metastasis (18). It has been reported that serum levels of E-selectin, ICAM-1, VCAM-1 analyzed in colorectal cancer were significant prognostic factors for patients survival, even though independent on tumor progression and metastasis (19). In metastatic prostate cancer, ICAM-1 and VCAM-1 seem to correlate with the metastatic stage while no differences were found between patients with localized cancer and controls (15). Our results are in accord with this assumption as we did not find, locally, a significant increase in ICAM-1, VCAM-1, P-selectin and E-selectin in patients affected by PCa (20). In our opinion, we suggest that it should be due to the restrict selection criteria, namely patients with a localized prostate cancer T2. Further, in relation with the pro-inflammatory pathway, we found IL-6 to be higher locally in PCa than in BPH patients (< 0.05) and systemically respect to controls.

On one hand, our study confirms that in localized prostate cancer, cellular adhesion molecules are not increased and they do not appear to be useful

in differencing localized PCa from BPH. On the other hand, we suggest that any selected serum markers may be of utility in evaluating tumor activity, for identifying metastatic potential or predicting progression. The identification of easily assessable circulating biomarkers, in patients who are likely to fail radical prostatectomy, might be of value to counsel them about the risk of biochemical recurrence. Toward this end, further studies on advanced prostate cancer are needed in evaluating more useful markers to predict metastasis and progression.

CONCLUSIONS

In BPH, inflammation may be taken into account in the correct selection of treatment choice as whether detected those patients should have a symptomatic beneficial improvement by adding anti-inflammatory drugs to standard therapies.

Changes of the inflammation and of the endothelial activation specific markers observed in patients affected by BPH and PCa may be not considered of value in discriminating those prostate diseases.

CONFLICT OF INTEREST

None declared.

ABBREVIATIONS

Benign prostatic hyperplasia: BPH
Prostate cancer: PCa
Interleukin-6: IL-6
CD40 ligand: CD40L
Endothelial-selectin: E-selectin
Platelet-selectin: P-selectin
Vascular cell adhesion molecule-1: VCAM-1
Intercellular adhesion molecule-1: ICAM-1
Standard error of the mean: SEM

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The one-stop clinic as the standard of out-patient care in a hospital urology department

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ABSTRACT

Purpose: To evaluate the performance of a 'one-stop' clinic in terms of proportion of discharges or inclusion in surgical waiting lists.
Materials and Methods: All patients were referred from primary care facilities (population 220.646) and from different departments in the hospital. Eight senior urologists, two registered nurses and two nurse attendants participated in the experience. Prior to the start of the project, referral protocols had been agreed with the primary care physicians involved. Compliance with the protocols was periodically tested. Eventually 5537 first visits (January-December 2009) where evaluable.
Results: Overall, the 'one-stop' format proved feasible in 74.2% of the patients (4108/5537). Patients, who successfully used the 'one-stop' format, were significantly younger than those who required additional consultations (43 vs 50 years old, respectively, Student's t test < 0.001).
For obvious reasons the 'one-stop' format was universally possible in male sterilization and penile phimosis patients. Similarly, the 'one-stop' policy was applied in most consultations due to male sexual dysfunction (75%) and urinary tract infection (73%). Other health problems, such as haematuria (62%) and renal colic (46%), required more than one visit so that care of the patient reverted to the traditional, outpatient care model.
Conclusion: A 'one-stop' philosophy is feasible for a number of procedures in a urological outpatient clinic. The costs to implement such an approach would be limited to managerial expenditure.

Key words: *day care; outpatients; primary health care; urology; clinic visit*
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INTRODUCTION

The Spanish National Health System (NHS) suffers an enormous stress. Average number of visits in 2008 was 9 per inhabitant, resulting in more than 400 million consultations (1). Such cyclopean duty is inevitably full of inefficiency: under the existing system it is not unusual that patients need to wait weeks for an appointment with their specialist. After the initial out-patient appointment, several visits are generally necessary prior to a management decision, as it is a standard procedure in Spain to perform diagnostic imaging and tests by appointment. Fortunately many urology departments have now their own endoscopy units and imaging facilities (echography). Nevertheless, follow-up visits are usually scheduled after the examinations have been carried out to discuss the diagnosis. The vast majority of patients need no further follow-up, but some enter into specific clinics for variable periods of time. To overcome these difficulties, the organizational reaction is to increase the size of the clinics, but in turn this response is likely, by weight of patient numbers, to decrease patient accessibility rather than increase it (2).

Nevertheless, accessibility is only a part of the problem; the current set-up lacks flexibility and creativity. An example would be the treatment

of well-defined urological problems, such as haematuria or scrotal swelling, which tend to require multiple visits (often 2 or 3, sometimes more) to the traditional urology outpatient clinic. During these visits, the patient will meet several different physicians, each having their own view of the patient's case. During this period of time, the patient must cope with his anxieties and fears until a final clinical decision can be made.

However, although improving patient accessibility and creating specific 'one-stop' clinics might be the answer for certain groups of patients (e.g. oncology cases), it can be argued that one-stop clinics have the potential to result in inequity, while not making sufficient improvement beyond that received by patients in the traditional model of specialized care.

The aim of our 'one-stop' programme was to provide all the services needed for patients referred to our facilities at a single visit.

The present study shows the results of a 'one-stop' clinic for all patients referred to the urology department of a 400-bed public hospital during 2009.

MATERIALS AND METHODS

We used the percentage of patients diagnosed and discharged, or diagnosed and included in the surgical waiting list (when indicated), as an indicator of the efficacy of the 'one-stop' approach.

There was not a formal 'one-stop' clinical setting or was the clinical setting specially designated. Simply, all patients referred to our facilities for a first consultation (irrespectively of their age, gender or reason for consultation) were processed using the 'one-stop' approach.

Patients were referred to our urological department from public primary care facilities (ten different public primary care centres, general population 220,646) and from other clinical departments in the Hospital Universitario de Fuenlabrada, Madrid, Spain. Three daily outpatient clinics were made available for these patients.

For patients referred from primary care, general practitioners (GP) were able to book patients directly into the 'one-stop' clinic. There were no formal restrictions for referrals. However, the Spanish NHS is not an open-access system, and GPs were expected to act as gate-keepers, i.e. to make clinical decisions about the suitability of patients for referral to secondary urological care.

For the study, referral criteria were agreed (3) and were periodically tested (4). Because the 'one-stop' approach was an initiative of the urology department, and customers (primary care and clinical departments in the hospital) have a passive role, there were no financial charges.

At the 'one-stop' clinic, the patient's basic clinical information could be accessed on-line. Once in our facilities, state-of-the-art diagnostic procedures where provided when needed.

Cases that finally resulted in inclusion in the surgical waiting list (WL) or discharge after a single visit were considered as managed under the 'one-stop' format. All other patients (i.e. patients needing another visit to the hospital for additional tests and/or urological work-up) were considered as managed under the traditional 'standard care' format.

Eight urologists, two registered nurses and two nurse attendants participated in the study. Registered nurses had previously been trained in basic urological echography, therapeutic endoscopy (pigtail removal) and urodynamics; they also had been given permission to conduct a minor surgery clinic (penile phimosis and male sterilization).

Ultrasound and endoscopy units were permanently operative and elemental urinalysis and plain abdominal films (KUB) were immediately available. Some minor surgical procedures (e.g. wound care, abscess drainage), uroflowmetry, urethral catheterization and urethral dilation were available in the outpatient clinic. However, non-conventional imaging and blood tests were not permanently available. Similarly, more elaborate minor surgical procedures, e.g. ultrasound-guided percutaneous nephrostomy, were not allowed in the 'one-stop' clinics.

Eventually, every urologist and nurse committed to achieving a minimum of 73% 'one-stop' cases. Doctors and nurses developed their own clinical responsibility and decided themselves upon the applicability of the 'one-stop' philosophy to the patient presenting to them. In general, when it was overwhelmingly clear that the 'one-stop' could not be supported (especially in cases requiring blood tests

or further imaging or pathology), a shift towards the standard approach was then decided. Thus, all patients were considered for the 'one-stop' approach until it became clear that a 'one-stop' approach was not sufficient and care of the patient then reverted to the traditional, standard approach.

For the present study, a total of 5537 first visits were considered. To approach the programme performance, the relationship between the consultation outcome ('one-stop' or 'standard care') and patient's age, gender, and reason for consultation was tested. More than 200 different reasons for consultation were recorded; for the purposes of conducting a reasonable statistical analysis, the reasons were summarized into 15 major arbitrary categories.

To decide about the overall programme efficacy, the number of revisits after discharge was considered.

Data were treated using the commercially available statistical program SPSS v11.5. The chi^2 and Student's t tests were used when appropriate. A 95% statistical significance was considered for all comparisons.

RESULTS

The average age of the patients (79.5% males) was 45 years (SD 18.7, range 1 month to 96 years). Table-1 shows the reasons for consultation grouped into the 15 major clinical syndromes. Overall, the 'one-stop' was achieved in 74.2% of the cases (4108/5537).

Eventually, it was observed that patients who were best able to take advantage of the 'one-stop' format were significantly younger than those managed under the 'standard' format (43 and 51 years, respectively, Student's t test < 0.001). A clear relationship between age group and the percentage of patients served with the 'one-stop' format was evident ($chi^2 < 0.001$), with 87% of patients younger than 15 years being managed under this format compared with only 62% of patients aged 66-75 years (Table-2).

The 'one-stop' format was achieved in a significantly higher percentage of men (75.8 and 67.9% of men and women, respectively, $chi^2 < 0.001$). Very significant differences ($chi^2 < 0.001$) were detected in the proportion of patients eventually served under the 'one-stop' format, according to the reason for consultation. For example, this was obviously going to be achievable with every case of penile phimosis and male sterilization referred to the clinic.

Similarly, the 'one-stop' approach was possible in the vast majority of consultations due to benign testicular conditions (82%), male sexual dysfunction (75%), urinary tract infection (73%) and bladder filling conditions (71%). In contrast, the 'one-stop' approach was not the rule for haematuria (38%), and achieved in only just over half of renal colic (54%), and genitourinary malformations (56%) (Table-3).

In comparison with the patients served with the 'one-stop' format, the proportion of patients served under the 'standard' approach, who were revisited shortly after their discharge was significantly higher (13.6 and 22.8%, respectively, $chi^2 < 0.001$). Average time to revisit was 102 days (SD 83.6 days, range 2 days to 339 days). Slight differences in time to revisit were present among patients served with the 'one-stop' format and under the 'standard' approach (95 and 113 days, respectively, Student's t test < 0.05).

DISCUSSION

Achieving effective and efficient health care in overcrowded, busy clinic settings is a common target of many health care systems. The present study represents an initiative in the field of non-selective prioritization models. Previous selective experiences (mainly focused in surgical patients), while potentially beneficial, have produced adverse effects, fundamentally in terms of inequity: where and how exactly is care being denied to others in order to provide access to the selected patients (2). To provide more efficient services the number of out-patient and investigation appointments have to be reduced (5).

During the present study we focused in reducing evitable appointments. When universally applied, access improvement strategies, such as the one presented here, provide very variable returns. Our study confirmed several assumptions. Considering the asymmetry in the distribution of urological conditions between men and women, and the high prevalence

Table 1 - *Reasons for consultation grouped into major syndromes.*

Reasons for consultation	*n*	%
Urological cancer (or suspected cancer)	421	7.6
Renal colic and/or urinary lithiasis	614	11.1
Acquired degenerative conditions of the genitourinary tract (urethral stenosis, acquired obstructive uropathy, and renal cysts)	68	1.2
Penile phimosis	423	7.6
Male lower urinary tract symptoms	211	3.8
Macroscopic and microscopic haematuria	177	3.2
Urinary tract infection	301	5.4
Disorders of bladder filling (urgency, incontinence, enuresis)	488	8.8
Malformations of the genitourinary tract	59	1.1
Non-neoplastic disorders of the male genitalia (penile pain, chronic prostatitis, hematospermia)	100	1.8
Male sterilization	483	8.7
Male sexual disorders (erectile dysfunction, premature ejaculation) and subfertility	380	6.9
Testicular pain, varicocele, hydrocele	385	7.0
Voiding dysfunctions unrelated to benign prostatic hypertrophy	358	6.5
Non-classifiable conditions	1069	19.3
Total	**5537**	**100.0**

Table 2 - *Relationship between age-group and type of approach ('one-stop' or standard care). In parentheses, percent.*

Age group	Approach, n (%)			Square chi test
	'One-stop'	Standard care	Total	
< 15	283 (87.3)	41 (12.7)	324	
15-25	397 (81.0)	93 (19.0)	490	
26-35	739 (78.7)	200 (21.3)	939	
36-45	821 (77.8)	234 (22.2)	1055	
46-55	804 (73.6)	289 (26.4)	1093	< 0.001
56-65	609 (67.1)	299 (32.9)	908	
66-75	253 (61.3)	160 (38.7)	413	
> 75	202 (64.1)	113 (35.9)	315	
Total	**4108 (74.2)**	**1429 (25.8)**	**5537**	

of some health problems in certain age-groups, the findings involving age and gender are not surprising: in general, the 'one-stop' approach was more frequently substantiated in males (with a high prevalence of consultations due to penile phimosis and male sterilization, both not needing extra consultations to gain a diagnosis). The 'one-stop' format was more successful in younger patients, who are usually referred for simpler consultations. Interestingly the 'one-stop' approach was progressively more dif-

Table 3 - *Relationship between clinical syndrome and type of approach ('one-stop' or standard care). In parentheses, percent.*

Reasons for consultation	**Approach, n (%)**			**Square chi test**
	'One-stop'	**Standard care**	**Total**	
Urological cancer (or suspected cancer)	242 (57.5)	179 (42.5)	421	
Renal colic and/or urinary lithiasis	331 (53.9)	283 (46.1)	614	
Acquired degenerative conditions of the genitourinary tract (urethral stenosis, acquired obstructive uropathy, and renal cysts)	40 (58.8)	28 (41.2)	68	
Penile phimosis	420 (99.3)	3 (0.7)	423	
Male lower urinary tract symptoms	145 (68.7)	66 (31.3)	211	
Macroscopic and microscopic hematuria	67 (37.9)	110 (62.1)	177	
Urinary tract infection	221 (73.4)	80 (26.6)	301	
Disorders of bladder filling (urgency, incontinence, enuresis)	349 (71.5)	139 (28.5)	488	< 0.001
Malformations of the genitourinary tract	33 (55.9)	26 (44.1)	59	
Non-neoplastic disorders of the male genitalia (penile pain, chronic prostatitis, hematospermia)	64 (64.0)	36 (36.0)	100	
Male sterilization	480 (99.4)	3 (0.6)	483	
Male sexual disorders (erectile dysfunction, premature ejaculation) and subfertility	286 (75.3)	94 (24.7)	380	
Testicular pain, varicocele, hydrocele	315 (81.8)	70 (18.2)	385	
Voiding dysfunctions unrelated to benign prostatic hypertrophy	240 (67.0)	118 (33.0)	358	
Non-classifiable conditions	875 (81.9)	194 (18.1)	1069	
Total	4108 (74.2)	1429 (25.8)	5537	

ficult to apply with male age; this trend with age was not found among women, perhaps due to the lack of feminine minor surgical conditions affecting younger women.

Conditions that were unlikely to require more than an empirical approach or simple diagnostic tests (i.e. echography, cystoscopy, elemental urinalysis), such as benign scrotal enlargement, male sexual dysfunction, urinary tract infection and bladder filling disorders, were mostly managed in a single visit. Similar results have been published elsewhere (6). Experiences in the field of cardiology have also resulted in excellent percentages of patients diagnosed and discharged after a single visit (7). Significant improvements in waiting times and patients' satisfaction are the rule (6,7). In our personal experience, 95.8% of the patients considered the 'one-stop' policy as 'adequate' or 'very adequate' in spite of the long transit times on the day of their visit (personal communication, data not published).

In summary, the need for histological and imaging studies were the main limitations for the 'one-stop' clinic. Nevertheless, this study proved that the 'one-stop' clinic can become the standard in urology. It can also be as robust as the traditional standard approach in terms of clinical effectiveness.

Interestingly, revisits (due to the original health problem) were less frequent among patients served under the 'one-stop' approach.

It should be stressed that communication abilities are very important when applying the 'one-stop' approach. The patient will only have a single contact with the urologist, so it is essential that communication is fluent and the patient has a clear clinical understanding of what has been decided. A detailed report should be offered to every patient at discharge. Another challenge with 'one-stop' clinics is the 'need' for a diagnosis: delivering a diagnosis in a matter of minutes can initially be difficult when one is not used to be profoundly operative. Professionals also need time to get used to the 'one-stop' model to feel confident and fully productive in using it.

The benefits for users seem clear: less appointments to gain a diagnosis, relationship with a single urologist, and avoiding the anxiety related to the delay of a firm diagnosis (6,8,9). Another intangible social benefit of the 'one-stop' approach is increased accessibility. Just taking into account, the echographies performed during the study period (1582), and assuming that the same number of follow-up visits were saved, a minimum of 1582 second-appointments slots were vacated. Currently, our outpatient clinic receives 60 new appointments and 21 follow-up visits per day. Saving 1582 follow-up visits means shortening the waiting list for a follow-up consultation by 75 days (13-15 weeks). According to the current fee system (personal communication, data not published), second visits in our department cost 59.64 euros. A formal cost-analysis of our policy was not undertaken, but on this basis savings for the Spanish NHS could approach 95,000 euros per year. Similar services have resulted in savings for other health systems (5).

Generalization of the 'one-stop' approach needs substantial cultural changes: the traditional format for a first-visit to the specialist in which typically diagnostic tests are ordered and a new appointment is scheduled must be replaced. Similarly, terms for referral and clinical protocols need to be developed and agreed. Facilities need to be professional and patient-friendly. Diagnostic units (echography and cystoscopy) should be permanently operative. As a 'side effect', the outpatient area becomes a very rigid structure were there is no room for unexpected, lengthy procedures (i.e., difficult urethral catheterization using multiple catheters and followed by suprapubic bladder drainage, or percutaneous ultrasound-guided nephrostomy).

Implementing the 'one-stop' clinic philosophy can result in serious stress for a clinical department because the condensation of activities can become very important. In such scenario, the staff require great versatility. In this field, nurse empowerment is crucial. It has already been proven that nurses can be very effective in gastrointestinal endoscopy, nuclear medicine, computed tomography, echography and mammography procedures (10-15). Because of their clinical training and basic skills and abilities, they represent ideal partners for urologists in a 'one-stop' clinic setting.

Outpatient policies in the Spanish public NHS need an urgent update. Our study represents an initiative in this field. Only free-of-cost organizational changes need to be implemented to switch from the standard, tedious, approach to the more vigorous and efficient 'one-stop' model.

CONCLUSIONS

The 'one-stop' format can be substantiated in most patients and should be the rule in urology clinics. The 'one-stop' format is exigent for professionals but the benefit in terms of reduction in the number of consultations is such that the 'pain' involved in making the change really is worth it.

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CONFLICT OF INTEREST

None declared.

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Vasectomy Occlusion Technique Combining Thermal Cautery and Fascial Interposition

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ABSTRACT

Introduction: Recent research on vasectomy shows that combining cautery and fascial interposition (FI) achieves the most effective occlusion of the vas and minimizes the risk of failure. We present a technique that combines cautery and FI and is suitable for low-resource settings.
Surgical Technique: The surgical technique consists of 1) exposing the vas with the no-scalpel approach; 2) cauterizing the epithelium of lumen of the vas using a portable battery-powered cautery device; 3) performing FI by grasping internal spermatic fascia and applying a free tie with suture material on the fascia to cover the prostatic stump of the vas and separate the two ends of the cut vas; and 4) excising a small 0.5 to 1 cm of the testicular stump.
Comments: To maximize vasectomy effectiveness, vasectomy providers should consider learning thermal cautery and FI to occlude vas deferens.

Key words: *vasectomy; vas deferens; cautery; urological surgery procedure; male; sterilization*
Int Braz J Urol. 2011; 37:630-635

INTRODUCTION

Recent developments in vasectomy have shown that: 1) the no-scalpel approach to expose the vas (known as the no-scalpel vasectomy, or NSV) reduces the risk of surgical complications over incisional techniques; 2) ligation of the vas and excision of a small segment between the ligatures (LE) is associated with an unacceptable risk of failure and should not be performed; 3) adding fascial interposition (FI) to LE reduces the risk of failure; and 4) cautery of the mucosa of the lumen of the vas combined with FI appears to achieve the most effective occlusion of the vas (1-3). Although NSV has been widely adopted (4,5), LE is still by far the most common vas occlusion technique performed in many parts of the world (5). Recently, the Program for Appropriate Technology in Health (PATH) recommended that FI and thermal cautery be introduced into existing and new vasectomy programs and that providers be trained in this method to maximize the cost-effectiveness of ongoing programs (6).

The surgical technique described below uses NSV (7) to expose the vas and the thermal mucosal cautery and FI occlusion technique to occlude the vas. This occlusion technique was originally described by Moss (8), who used metal clips to perform FI. It has since been performed with a very high rate of success in thousands of men (9,10). In the technique described, the metal clip is replaced by a free tie on the vas sheath (see step 9 of the surgical technique). Although this adaptation of Moss's technique can be employed in any setting, it is particularly suitable for low-resource settings where silk thread is already commonly used to ligate the vas (5) and where metal clips or other options to perform FI -such as sterile suture material mounted with a needle (11)- are not available. This is the case in

many Asian countries (5) and may also be the case in Africa and Latin America. The only material that the new technique needs, in addition to the instruments and material already required to perform NSV and LE, is a portable battery-powered thermal cautery device. This kind of device is available from various suppliers (e.g. www.ameditech.com, www.vasectomy.ca, www.instrumedindia.com) and is easier and much more convenient to use than an electrical cautery device because of its small size and the absence of wires.

SURGICAL TECHNIQUE

1. Expose the vas outside the scrotum using the NSV technique. The NSV technique is described in detail elsewhere (7).
2. Completely separate the sheath (internal spermatic fascia) from the exposed segment of the vas (Figure-1).
    a. Tip: Make sure only a partial thickness of the vas is grasped - do not encircle the vas with the ring forceps - otherwise control of the vas will be lost when it is cut.
    b. Tip: The length of the bare vas segment does not need to be as long as when using the LE technique. When stripping the sheath, open the blades of the dissecting forceps 3 to 5 mm, i.e., less than half of the length used for LE.

Figure 1 *- Opening the dissecting forceps to strip the sheath.*

3. Hemi-transect the prostatic end of the bare vas at mid-distance between the ring clamp teeth and the remaining vas sheath.
    a. Tip: The cut must be deep enough to expose the lumen but the posterior wall of the vas should remain intact.
    b. Tip: Hemi-transection may be performed with small sharp scissors or with the thermal cautery device (Figures 2 and 3).

Figure 2 *- Hemi-transecting the vas with scissors.*

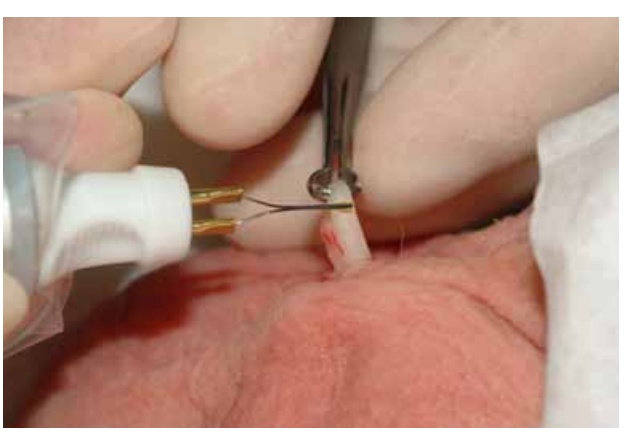

Figure 3 *- Hemi-transecting the vas with a thermal cautery device.*

4. Insert the cold cautery tip into the hemi-cut towards the lumen of the prostatic vas. Then bring it parallel to the vas while fully inserting the tip into the lumen.

   a. Tip: Verify that the device is functioning properly before starting the procedure. The tip must become red when the device is turned on.
   b. Tip: Do not insert the tip into the lumen when the device is turned on. The tip should be cold when inserted.
   c. Tip: Hold the device like a pencil and stabilize it using the thumb of the other hand.
   d. Tip: Make sure the tip is inside and parallel to the lumen before turning on the device.
5. Turn on the cautery device for 2 to 3 seconds, until the vas just starts to become opaque or fumes appear (Figure-4).
   a. Tip: Take care not to over-burn the vas. Only the epithelium must be destroyed: not the muscular vas wall.
   b. Tip: Cautery time varies with battery strength. Cautery with brand-new alkaline batteries may only take 1 second.
   c. Tip: The tip may stick into the vas. Gentle traction on the tip with a rotating movement should help deliver the tip from the lumen. Turning on the device for another second while pulling the device out may help. Again, take care not to burn the vas excessively.

Figure 4 *- Cauterizing the epithelium of the lumen of the prostatic segment of the vas.*

6. Completely transect the vas using scissors or the heated cautery device (Figure-5).
   a. Tip: Complete the cut exactly at the site that has been hemi-transected.
   b. Tip: Do not apply traction on the ring forceps -the testicular stump- while cutting the vas. Traction may cause the prostatic stump to slide too deeply into the scrotum.

Figure 5 *- Cutting the vas with a thermal cautery device.*

7. To cover the prostatic stump, use the dissecting forceps or small tooth forceps (Adson) to grasp the full thickness of the sheath (internal spermatic fascia) at mid-distance between where the fascia sticks to the testicular vas segment and the prostatic stump (Figure-6).

Figure 6 *- Grasping the internal spermatic fascia with dissecting forceps.*

a. Tip: If the prostatic stump does not slide spontaneously into its sheath, do one of the following actions until the vas slides into its sheath:
    i. Make sure the posterior wall of the vas (including its sheath) has been completely transected by very gently making a further cut with the cautery device. After adequate transaction, a loop will no longer be observed (Figure-5).
    ii. Gently use the dissecting or tooth forceps to push the prostatic stump into its sheath.
    iii. Pinch the fascia over the stump with thumb and index finger.
b. Tip: When grasping the fascia, make sure to grasp both sides of the sheath in order to cover the prostatic stump.
c. Tip: Grasping the fascia too high or too low prevents adequate full coverage of the stump.

8. Holding the fascia firmly with the dissecting forceps or the tooth forceps, gently pull the testicular end away in order to separate 2-3 mm of the fascia covering the testicular segment (Figure-7). This step is essential to ligating a portion of the fascia that covers the testicular stump along with the fascia that covers the prostatic stump and thereby performing adequate FI (see Step 9).

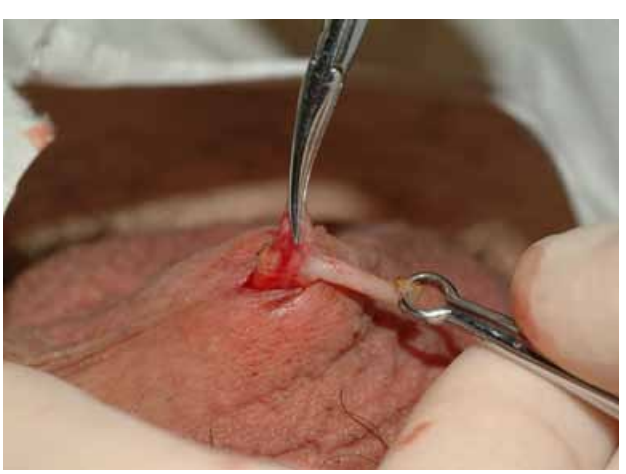

Figure 7 *- Pulling on the testicular stump to completely separate the sheath covering the testicular stump.*

9. Put a 2-0 or 3-0 silk (or other suture material) free tie with at least 3 knots on the fascia overlying the prostatic stump (Figures 8 and 9).
    a. Tip: Make sure that a portion of the fascia covering the testicular segment is ligated over the prostatic stump.
    b. Tip: Vessels may be ligated concomitantly to control bleeding.
    c. Tip: Make sure that only the fascia and not the prostatic stump is ligated.
    d. Tip: Ligation of the fascia may help to completely push the prostatic stump into the fascia if this was not adequately achieved in Step 7: see Tip a.

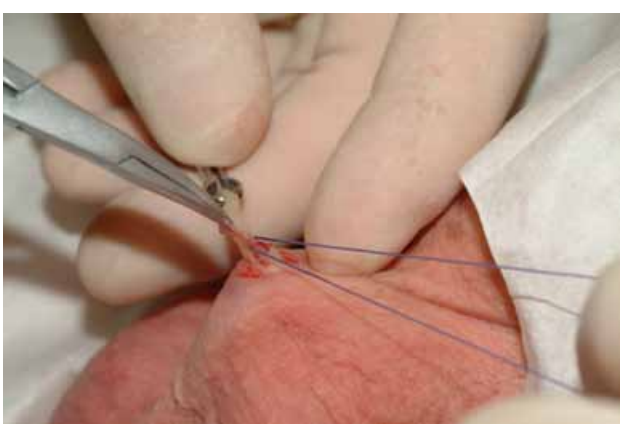

Figure 8 *- Ligating the fascia over the prostatic stump (1).*

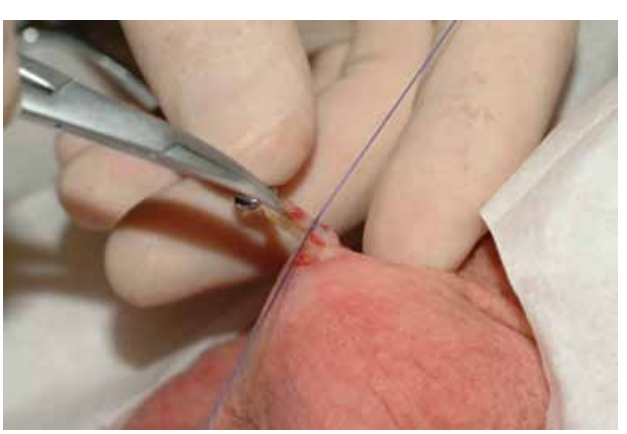

Figure 9 *- Ligating the fascia over the prostatic stump (2).*

10. Cut the threads.
11. Hemi-transect the testicular end of the vas to leave a segment of about 0.5 to 1 cm grasped into the ringed clamp. This segment will be excised.

12. Repeat Steps 4 to 6 on the testicular end (Figure-10).
    a. Tip: Before excising the vas segment and letting the prostatic and testicular vas stumps slip into the scrotum, check carefully for bleeding.
        i. Use the cautery device to control minor bleeding.
        ii. A suture over the fascia at the base of the testicular segment may control persistent bleeding.

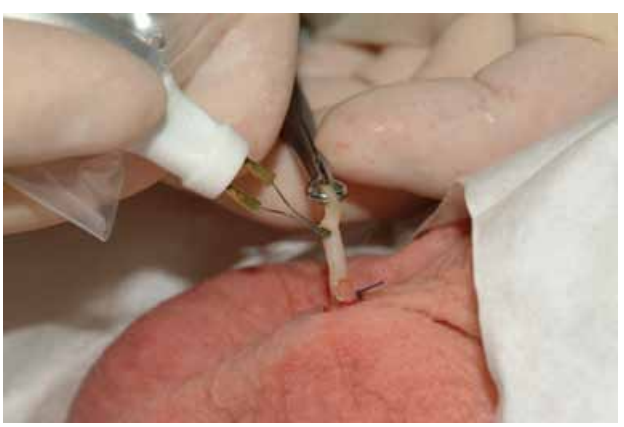

Figure 10 *- Cauterizing the lumen of the testicular stump after completing FI on the prostatic stump.*

Note: The testicular end may be left open ("open-end vasectomy") by completely transecting the vas with scissors at Step 11 and omitting Step 12. In this case, check carefully for any bleeding before cutting the vas and letting it slip into the scrotum.

13. Repeat the procedure on the contralateral vas.

COMMENTS

A video of this surgical technique may be viewed at www.youtube.com/watch?v=Pw80QNbnVig. Pilot assessments in many countries in Asia (5), in Rwanda, and in Canada showed that this technique can be safely and effectively performed by new vasectomy providers and surgeons who already perform vasectomies. Nevertheless, there may be barriers to implementing this technique on a large scale in low-resources settings. Direct costs (cautery devices, tips, and batteries) and indirect costs (training, processing, and the maintenance of the devices) would need to be considered. However, the Program for Appropriate Technology in Health (PATH) has determined that cautery handles and tips currently available in the United States and Canada are durable and can be safely reused, and that the proposed technique would be cost-effective in various low-resource settings (6). For this reason, new vasectomy providers and surgeons who already perform vasectomies using LE should consider learning thermal cautery and FI to occlude vas deferens in order to maximize the effectiveness of the procedure.

CONFLICT OF INTEREST

None declared.

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Percutaneous Intervention of Large Bladder Calculi in Neuropathic Voiding Dysfunction

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ABSTRACT

Purpose: To report our results and rationale for treating large bladder calculi in patients with neuropathic voiding dysfunction (NVD) using percutaneous cystolithalopaxy.
Materials and Methods: Ten patients with a previously diagnosed NVD presenting with a large stone burden were identified from our department database and a retrospective review of case notes and imaging was performed.
Results: Percutaneous access to remove bladder stones (range 8x7 to 3x2 cm) had a mean surgery length of 150 min and blood loss of 23 mL. Six of the seven patients treated percutaneously were discharged on the day of surgery and suffered no complications, while one patient experienced poor suprapubic tube drainage and required overnight admission with discharge the following day. Transurethral removal of stone burden (range 4x4 to 4x3 cm) had a mean surgery length of 111 min and blood loss of 8 mL. Each of these three patients were under our care for less than 23 hours, and one patient required a second attempt to remove 1x0.5 cm of stone fragments. There was no statistical difference between mean operative times and estimated blood loss, $p = 0.5064$ and $p = 0.0944$ respectively, for the two treatment methods.
Conclusion: In this small series, percutaneous cystolithalopaxy was a safe, effective, and often preferred minimally invasive option for removal of large calculi in patients with NVD. We suggest possible guidelines for best endoscopic approach in this population, although a larger and prospectively randomized series will be ideal for definitive conclusions.

Key words: *urinary bladder; calculi; neurogenic; laparoscopy; lithotripsy*
Int Braz J Urol. 2011; 37: 636-641

INTRODUCTION

Bladder stones are a well-recognized late complication of NVD, including those who have undergone prior bowel to bladder reconstruction. Reported risk factors for developing bladder stones include patient age, type of augmented diversion, immobilization contributing to hypercalciuria and oxalate calcium stone formation, and infected urine (1-3). Infection of the urine may be secondary to urinary stasis with incomplete emptying, repeated instrumentation or catheterization, and foreign bodies, such as mucous, hair, or amorphous sediment (4,5).

Neuropathic conditions causing decreased patient sensitivity often permit calculi to develop without complaint until the burden becomes numerous, large, and painful. Prior bladder augmentation and a large stone burden can cause the removal of calculi to be more challenging. Comparison of approaches to remove bladder stones of a small size have indicated percutaneous and endoscopic techniques to be more advantageous than open cystolithotomy in terms of shorter hospitalization periods, less postoperative morbidity, and minimal damage to blood flow of intraperitoneal tissue (6).

However, current literature describing the optimal approach to large bladder stones in patients with NVD is lacking. We hypothesize that in this patient population, a minimally invasive technique would be beneficial as it reduces risk to the patient's internal anatomy, which is often distorted due to previous surgeries, manipulation, or their NVD condition. When taking into consideration each patient's

unique complexities, as well as the various sizes of calculi, the most favorable endoscopic approach in patients with NVD has yet to be explored. Thus, with the goal of reducing morbidity, we report our results and rationale for using percutaneous cystolithalopaxy as an intermediate step for stones too large or inappropriate for transurethral management, and as an attempt to avoid open surgical removal in a complex NVD population with large vesical calculi.

MATERIALS AND METHODS

Ten patients (four male and six female) with previously diagnosed NVD who also presented with bladder stones between 2005 and 2009 were identified from our departmental database, and case notes and available images were reviewed retrospectively. We assessed the neuropathic history, prior bladder surgeries and complications, and urodynamic findings of each patient. We then compared the stone burden, surgical procedure and any encountered complications to remove the calculi, length and details of surgery, length of hospital stay, and recurrence. The ten patients were organized retrospectively into two groups based on the procedure performed.

Group 1 consisted of patients that had undergone cystolithalopaxy through a percutaneous suprapubic approach. In this group, percutaneous suprapubic access was gained either through an old suprapubic tract scar, at a new site if judged safe based on exam and cystoscopy, or under CT guidance when deemed too high of a risk to perform otherwise. The tract was dilated with standard balloon dilatation routinely used for percutaneous nephrolithotomy procedures, and a 30 french Amplatz sheath was left in situ for direct access to the bladder during the procedure. Depending on the stone characteristics; pneumatic, ultrasonic, and holmium laser tools were used to fragment and then irrigate the calculi under direct visualization via rigid and flexible nephroscopy. After clearance of all calculi, the instruments were removed and a 16 french suprapubic catheter was left to gravity drainage. The suprapubic tube was removed in the office at post-operative follow-up if it was not to be used for continued management of the patient's NVD.

Group 2 consisted of patients that had undergone cystolithalopaxy via their native urethra. In these patients a holmium laser was utilized to fragment the stones via flexible and rigid Cystoscopy with 16-24 french instruments. The fragments were then irrigated and evacuated through the urethral sheath. In patients with an augmented bladder and catheterizable stoma, the catheterizable limb was never used as a channel to remove calculi. Patients with smaller urethral outlets, prior hypercontinent sling, or prior bladder neck closure, were all approached percutaneously. The rationale to utilize a suprapubic site versus the urethra as the conduit for stone extraction was then analyzed.

RESULTS

Of the ten patients who presented with NVD and concurrent bladder calculi, the NVD diagnosis was attributed to spina bifida in five patients, traumatic brain or spinal cord injury in three patients, congenital bladder exstrophy in one patient, and chronic urinary retention in one patient with a congenital connective tissue disorder. Five of the ten patients had also undergone previous enterocystoplasty bladder augmentation with formation of a catheterizable stoma, including the patient with congenital bladder exstrophy (Table-1). At the time of stone removal the mean age of the ten patients was 31 years (range 19-57).

Percutaneous stone extraction was performed on a total of seven patients (70%), with stone size ranging from 8x7 to 3x2 cm. Three of the patients, with stone burdens of 4x4, 4x3, and 3x2 cm, had a patent urethra and a pre-existing suprapubic tube in place prior to discovery of the bladder calculi. The patient with congenital bladder exstrophy had an 8x7 cm stone burden and a history of multiple bladder surgeries resulting in an enterocystoplasty bladder augmentation and closure of the bladder neck. The three other patients, two of which had previous enterocystoplasty bladder augmentations, all had patent urethras, no pre-existing suprapubic tubes, and stone burdens of 6x2, 6x5, and 7x7 cm. Six of the seven patients treated percutaneously were discharged on the day of surgery and suffered no complications, while one patient experienced poor suprapubic tube drainage and required an overnight

admission. No complications were observed after discharge from the hospital. The average length of surgery to remove large bladder calculi via cystolithalopaxy through a percutaneous suprapubic approach was 150 minutes (range 35 - 260 min.) with a mean estimated blood loss of 23 mL. No patient in this group required a second attempt to remove remaining fragments, nor did any patient experience bowel injury while creating the percutaneous access or at anytime throughout the procedure.

Group 2 consisted of three patients (30%), none of which had a pre-existing suprapubic tube in place. One patient had a 4x3 cm stone burden with no previous bladder surgeries, while the other two patients both each had a 4x4 cm stone burden and an augmented bladder and catheterizable stoma. One of these last patients required a second attempt two weeks after the initial process to extract remaining fragmented stones, totaling 1x0.5 cm, which could not be removed during the first procedure. Each of

Table 1 - *Patient characteristics.*

Pt #	Neurogenic History	SPT	Size (cm)	Past Bladder Surgery	Patent Urethra	Approach
1	Bladder Extrophy	Yes	8x7	Enterocystoplasty bladder augmentation with subsequent revision, bladder neck closure, ureterectomy	No	Percutaneous
2	Spina Bifida	No	7x7	Enterocystoplasty bladder augmentation with catheterizable stoma	Yes	Percutaneous
3	Traumatic SCI	No	6x5	No	Yes	Percutaneous
4	Spina Bifida	No	6x2	Enterocystoplasty bladder augmentation, bladder neck reconstruction with hypercontinent sling	Yes	Percutaneous
5	Traumatic SCI	Yes	4x4	No	Yes	Percutaneous
6	Spina Bifida	No	4x4	Enterocystoplasty bladder augmentation with catheterizable stoma	Yes	Urethra
7	Spina Bifida	No	4x4	Enterocystoplasty bladder augmentation with catheterizable stoma	Yes	Urethra
7 (2)	Spina Bifida	No	1x0.5	Enterocystoplasty bladder augmentation with catheterizable stoma	Yes	Urethra
8	Spina Bifida	Yes	4x3	No	Yes	Percutaneous
9	Traumatic SCI	No	4x3	No	Yes	Urethra
10	Chronic UR	Yes	3x2	No	Yes	Percutaneous

cm = centimeters, Pt = patient, SCI = spinal cord injury, SPT = suprapubic tube, UR = urinary retention

these patients was under our care for less than 23 hours. Patients that had undergone cystolithalopaxy via their native urethra had an average length of surgery, including second attempts, of 111 minutes (range 38-250 min.), and a mean estimated blood loss of 8 mL. After the procedure, there was no reported increase in incontinence through the urethra, and no urethral strictures or other complications possibly due to the surgery were observed in this patient population. Using a two-sample t-test, statistical comparison of mean operative times and blood loss between a percutaneous and transurethral approach yielded no significant difference, $p = 0.5064$ and $p = 0.0944$ respectively.

DISCUSSION

Patients with NVD are at a higher risk of calculus formation. Those who have undergone prior enterocystoplasty have reported incidences of bladder calculi as high as 50% (7). The etiology of bladder stone formation appears to be multifactorial, with urinary stasis likely the most significant factor. We stratified our patients with bladder calculi in terms of stone burden, history of lower urinary tract surgeries, and presence of a native urethra, suprapubic tube, and catheterizable stoma. Our goal in stratification is completing stone removal in a single operative procedure and with the least amount of operative time, while minimizing morbidity and returning the patient to baseline function as rapidly as possible.

Our retrospective review of this small case series allows recommendations to be generated regarding percutaneous versus native urethral approach in NVD patients with a large stone burden. In this patient population, the presence of a pre-existing suprapubic tube provides an easily accessible tract that could be utilized to gain access percutaneously, minimizing the inherent risks associated with initial percutaneous access to the bladder. If there is no suprapubic tube present, it is then important to consider the size of the stone when determining if a percutaneous procedure is appropriate. Retrospective analysis of our data indicates that with a stone burden greater than 4 cm, a percutaneous approach was the procedure of choice (Figure-1). When choosing the suprapubic site, prior imaging, physical exam findings, and cystoscopy were utilized to minimize risk of injury to bowel or major vascular structures. It is

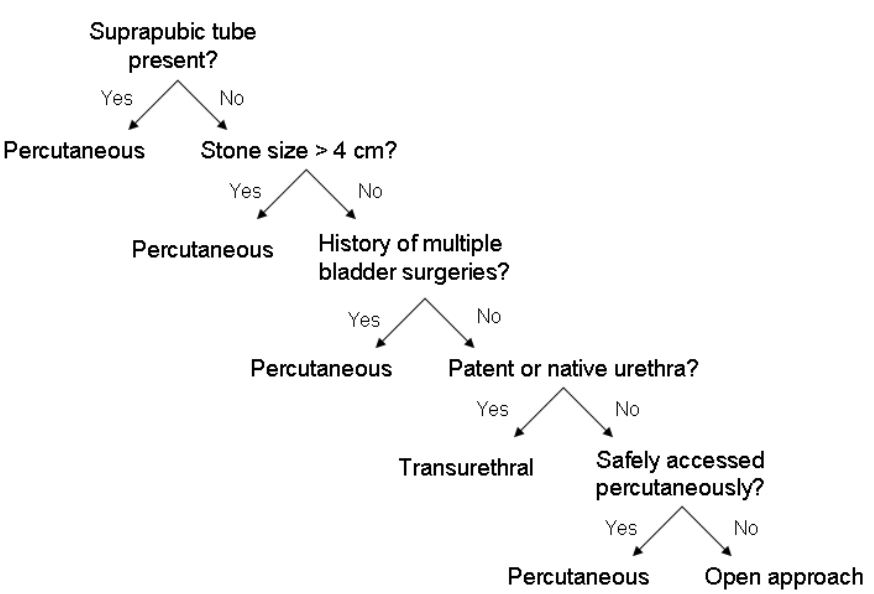

Figure 1 *- Recommendations for percutaneous treatment of large bladder calculi in patients with neuropathic voiding dysfunction.*

recommended that CT guided access be considered in patients who are at high risk for bowel injury, such as those with prior enterocystoplasty and/or multiple prior open surgical procedures. In our patient population, CT scan was used to obtain access in one patient who was born with bladder exstrophy and had a history of multiple prior surgeries, including bladder closure with pubic symphysis reapproximation and placement of a colonic reservoir that was subsequently revised.

A transurethral approach to remove bladder calculi was performed on three patients with stone burdens of 4x3, 4x4, and 4x4 cm. One of the three required a second "look", or follow-up surgical procedure, to extract remaining fragments. None of the patients in this group had a pre-existing suprapubic tube, and all had a patent urethra.

In our experience, patients with a patent and non-reconstructed native urethra/bladder neck who presented with calculi less than 4 cm were well managed with a transurethral approach. However, those with a stone burden greater than 4 cm in a single dimension and/or coexistence of the prior lower urinary tract surgeries discussed above were chosen to be managed percutaneously. This 4 cm cutoff was initially an arbitrarily assigned volume based on the author's experience that larger stone volumes would potentially take excessive operative time if performed transurethrally. Although the average length of surgery was greater in the percutaneous group (150 min.) compared to the transurethral group (111 min.), the difference in operative times was not statistically different ($p = 0.5064$). Similarly, the observed difference in the mean estimated blood loss, 23 mL for group 1 and 8 mL for group 2, is also determined to not be statistically significant ($p = 0.0944$). Furthermore, the lack of complications and postoperative morbidity observed in both groups continues to demonstrate safety for either approach.

Patients with multiple prior lower urinary tract procedures and a large stone burden, present with a potentially very complex scenario which must give the surgeon reason to pause and consider the best approach to take. When initially presented with a complex NVD patient, the decision to undergo a transurethral versus percutaneous approach was based on the amount of time it would likely take to fragment the stone. Our 10 patient sample series demonstrates that it is effective and safe to utilize a percutaneous approach on patients with stones greater than 4 cm. However, as we never attempted to utilize a transurethral approach on stones of this size, we cannot conclude that stones greater than 4 cm cannot also be treated transurethrally.

Initially, we also made the decision to attempt a minimally invasive approach instead of an open procedure for complicated NVD patients with large vesical calculi. This was based on the work of Docimo et al., who compared open and percutaneous cystolithotomy and reported less postoperative morbidity and similar stone recurrence rates between the two groups (6). We observed similar findings as six (86%) of our patients in the percutaneous approach group had a hospital stay of less than 23 hours and only 1 (14%) patient required overnight admission. Open surgery has the inherent risks of extended hospitalization, prolonged catheterization, and an increased risk of infection (8). Although not compared directly, the lack of complications and morbidity that we observed with the percutaneous approach leads us to believe that percutaneous intervention for patients with NVD and large bladder calculi is an acceptable alternative to open cystolithotomy. Percutaneous intervention avoids urethral manipulation and consequently stricture, and the large Amplatz sheath allows larger fragment removal as well as improved visibility by superior irrigation, thus leading us to believe that it is a lower risk procedure in this specific patient population (9-11). Nonetheless, further investigation is warranted to directly compare percutaneous and open procedures in patients with NVD and large vesical calculi.

CONCLUSIONS

In this small series, percutaneous cystolithalopaxy is a safe and under certain circumstances, a more beneficial alternative to a transurethral approach or perhaps even open cystolithotomy in patients with NVD and large bladder calculi. Ret-

rospective analysis of our experience demonstrates that percutaneous cystolithalopaxy was a safe and effective method of choice in patients with a pre-existing suprapubic tube, stone size greater than 4 cm in any single dimension, a history of prior bladder surgery, or in the absence of a patent urethra. We suggest possible guidelines for utilizing a percutaneous approach in this population in place of an open or transurethral procedure, although a larger and prospectively randomized series will be ideal for definitive conclusions.

ABBREVIATIONS

cm = centimeter
CT = computed tomography
min = minute
mL = milliliter
NVD = neuropathic voiding dysfunction
Pt = patient
SCI = spinal cord injury
SPT = suprapubic tube
UR = urinary retention

CONFLICT OF INTEREST

None declared.

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Botulinum Toxin A for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients

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ABSTRACT

Purpose: Neurogenic detrusor overactivity (NDO) is common in patients who suffer from multiple sclerosis (MS). When the usual pharmacological treatment fails, botulinum toxin type A (BTX-A) injections can be proposed. The safety and efficacy of this treatment are already well known, but only a few studies focus on its use in patients with MS.
Materials and Methods: Seventy-one patients with MS underwent their first BTX-A injection for refractory NDO. They had clinical and urodynamic cystometry assessment before and three months after injection. The patients were divided in three groups according to treatment efficacy: full success (total urinary continence, no overactive detrusor), improvement, or total failure (urge incontinence and overactive detrusor).
Results: 77% of the patients had clinical improvement or full success of the treatment with a reduction of their urgency and incontinence. Significant urodynamic improvement after treatment was shown on different parameters: volume at first involuntary bladder contraction ($p = 0.0000001$), maximum cystometric capacity ($p = 0.0035$), maximum detrusor pressure ($p = 0.0000001$). 46% of the patients were in the "full success" group. 31% of the patients had a partial improvement. 23% of the patients had no efficacy of the treatment. Duration of MS was a predictive factor of treatment failure ($p = 0.015$).
Conclusions: Despite that a full success was obtained in 46% of the cases, BTX-A injection therapy failed to treat refractory NDO in 23% of patients suffering from MS. Duration of the disease was a predictive factor for an inefficient treatment. The injection therapy should be considered as soon as oral anticholinergic drugs fail to reduce NDO.

Key words: *kidney; multiple sclerosis; botulinum toxins; urinary bladder; neurogenic; administration; intravesical; treatment outcome*
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INTRODUCTION

Multiple sclerosis (MS) is a common demyelinating disease of the central nervous system. The lesions occur in different time and localization in subcortical areas, brain stem and spinal cord. The disease has varied clinical presentations (1). Bladder and urethra dysfunction are very common. Detrusor overactivity is the most common urodynamic sign. It is observed in 44% (2) to 81% (3) of patients. Detrusor sphincter dyssynergia is associated with overactive detrusor in 93% of cases (2).

Detrusor overactivity is often associated with overactive bladder, defined by urgency, possibly associated with urge incontinence, daytime frequency, and nocturia (4). These symptoms significantly alter the quality of life (5). Urological complications including hydronephrosis, vesicoureteral reflux, urosepsis, and urolithiasis (6) occur in 12% of the patients who suffer from neurogenic detrusor overactivity (NDO) and MS (7). The rate

of upper urinary tract involvement is lower in patients with MS than in patients with spinal cord injury (SCI), without a clear explanation (8).

Anticholinergic agents are the first line of treatment for NDO. If not sufficient, a combination of anticholinergic agents therapy can be tried (6). Anticholinergic agents can cause side effects that forbid their use, as on the central nervous system (memory and cognition alteration) or on the heart (prolongation of QT interval) (9). Electrical stimulation is an alternative, but often insufficient (8). When usual treatments fail, the NDO is considered as refractory, and the use of bladder botulinum toxin-type A (BTX-A) injection is nowadays recommended with a good level of proof (10). BTX-A formulation Botox is usually used. The efficacy of this treatment versus placebo (11) and resiniferatoxin injection therapy (12) has been demonstrated. Gomes et al compared the use of two different BTX-A formulations (Botox® and Prosigne®). Botox treatment resulted in significantly greater increase of urodynamics parameters, and a tendency for better results in terms of continence rate (13).

In patients suffering from NDO, the use of intra detrusor BTX-A injection improves continence in 60% to 80% of the patients, with total continence in 42% to 87% of the patients. Quality of life is improved in 35% to 65% of the patients (14). Up to 70% of patients stop their anticholinergic drugs after BTX-A treatment (15). BTX-A bladder injection reduces the incidence of symptomatic urinary tract infections (16). The effect lasts between six and 12 months in smooth muscle, such as the bladder (6,17). In the literature, the populations studied are mostly composed of patients suffering from SCI (57%) and fewer patients suffering from MS (17%) (14). Reports focused on the use of BTX-A bladder injection therapy in NDO due to MS are sparse (18). In three studies, clinical and urodynamical efficacy of BTX-A therapy in patients suffering from NDO in MS has been shown (19-21).

The objective of the present report is to evaluate the clinical and urodynamical response to the first BTX-A injection of patients suffering from refractory NDO in MS.

MATERIALS AND METHODS

After local ethical committee approval, 71 patients suffering from MS and complained of urgency, daytime frequency and urge incontinence due to refractory NDO were included in the study. NDO was considered as refractory when at least two anticholinergic agents each taken correctly for at least two months followed by an association of these two agents for at least two months failed to reduce clinical and urodynamical symptoms.

All the patients received their first BTX-A bladder injection. Anticholinergic medications that would interfere with urovesical function were stopped at least one week before BTX-A injection.

Data were collected with a retrospective methodology.

Technique

The absence of urinary tract infection or any anticoagulant treatment were checked before the injection. For each patient a dose of 300 UI of BTX-A (Botox®) diluted in 30 mL of saline was injected in thirty detrusor sites sparing the trigone, during a cystoscopy. Analgesia by inhaled nitrous oxide (Kalinox®) was always proposed, in order to avoid pain during injection.

All the patients were able to practice intermittent self-catheterization (ISC) before the injection therapy, to manage the possible increase of post-void residual volume after injection.

Evaluation

The patients had clinical and urodynamic assessment one month before and three months after BTX-A injection. Two weeks before treatment, the patients were trained in ISC, by a nurse. Later examinations were not reported, as this study focuses on the response to the treatment. Urodynamic investigations were done complying with ICS recommendations (17).

Age, sex, and the time interval since the first neurological symptoms occurred was noted for each patient.

Before each visit the patients made a bladder diary during three days, as described by Abrams (4). The mean number of urge urinary incontinence episode was estimated for each patient, at each visit.

Urodynamic data were collected: volume at first involuntary bladder contraction (FCV), maximal detrusor pression during filling (P det. max.), maximal cystometric bladder capacity (MCC).

Treatment efficacy was judged three months after the first injection. Patients were sorted into three groups, according to the result of the treatment. The first group is the "full success" group, in which urge urinary incontinence totally disappeared and urodynamic assessment demonstrated no involuntary bladder contraction. In the second group, called the "improvement" group, the patients described a reduction of 50% of urge urinary incontinence episodes. The urodynamic parameters were improved: FCV and MCC were at least 50% higher, and P detmax decreased at least 50%, compared to the pre treatment evaluation. The third group was called "total failure" group, as the patients complained of unchanged incontinence, and/or urodynamic assessment was similar to the first one.

Statistics

The Student t-test was used to compare means of values with Gaussian distribution. The chi-square test was used to compare independence of parameters. The significance was assumed if $p < 0.05$.

RESULTS

Fifty-two women and 19 men were studied, with a mean age of 47.6 years (standard deviation -SD:11.2). 66 patients (93%) complained of urgency with urge incontinence associated with slow or intermittent stream. For these patients, the initial urodynamic assessment showed detrusor overactivity and detrusor sphincter dyssynergia. Out of them, 64 patients practiced non-exclusive intermittent self-catheterization, and two had total urinary retention requiring exclusive intermittent self catheterization. Five patients (7%) complained of urgency and urge incontinence, due to detrusor overactivity without detrusor sphincter dyssynergia.

The injection therapy improved significantly FCV, MCC, and P det. max. (Table-1) All of the patients needed intermittent self-catheterization after injection. No other relevant side effect was observed.

After BTX-A injections, 55 patients (77%) had a significant clinical improvement, with a decrease of their daily urge incontinence of at least 50%. Among those patients, 33 had a total continence, and no involuntary bladder contraction on urodynamical assessment. These patients (46%) were assigned to group 1, the "full success" group. Twenty-two patients (31%) were assigned to group 2, "improvement". Sixteen patients (23%) were assigned to group 3, "total failure" (Table 2).

Table 1 *- Global results. Urodynamics efficacy of the injection therapy in 71 patients with MS and refractory overactive detrusor.*

	Before injection	**After injection**	**p**
Mean FCV (mL) / *SD*	159 / 83	301 /120	$p < 0.001$
Mean MCC (mL) / *SD*	240 / 130	328 / 114	$p < 0.001$
Mean P det. max. (cm H_2O) / *SD*	61 / 23	36 / 27	$p < 0.001$

Table 2 *- Group analysis: repartition of the patients and demographic data.*

	Full Success	**Improvement**	**Failure**	**Statistics : p**
Number of patients/ ***%***	33 / 46%	22 / 31%	16 / 23%	
Sex	25 women 8 men	15 women 7 men	12 women 4 men	P = 0.81
Mean age (years) / *SD*	47 / 10.4	46 / 12.1	50.6 / 11.5	P = 0.22
Mean duration of MS (years) / *SD*	13.8 / 9	11.7 / 9	19.6 / 12.4	P < 0.05

There was no statistical difference in the three groups concerning demographic data, or urodynamic parameters before injection.

In group 3 the duration of the disease was significantly longer than in the other two ($p < 0.05$). Therefore duration of the disease seems to be a predictive factor for treatment failure (Table 2 and 3).

DISCUSSION

The overall results of our study are consistent with previous reports, in terms of safety and efficacy of BTX-A treatment. Moreover, BTX-A bladder injections have comparable efficacy to treat NDO in patients suffering from SCI or from MS. Indeed, the overall efficacy of the treatment in SCI patients varies from 75% to 90% (22-24), which is consistent with 77% of efficacy of treatment in the present study.

Only three studies, of 16 patients (19), 43 patients (20), and 12 patients (21), focus on MS patients. In these reports, as in the present one, clinical and urodynamic parameters were significantly improved by the treatment. Despite these excellent outcomes, not all of the patients were efficiently treated. This was consistent with 27.9% of the patients who needed anticholinergic medication in association with BTX-A therapy in the study by Kalsi (20).

In our study duration of MS was a predictive factor for failure of BTX-A treatment. A worsening of neurological and urinary conditions was associated with the duration of MS (2) and seemed to result in a more severe NDO than in the early stage of the disease. As the neurological condition progresses, the severity of the urinary symptoms increases (8), and renal complications of NDO are more frequent (3). This result is an argument for an earlier proposal of BTX-A injection therapy in refractory NDO due to MS. However, the study on rats from Temeltas did not find any histological difference of the bladder tissue after BTX-A injection either if the injection was

Table 3 *- Group analysis. Mean urodynamic criteria before injection.*

	Full Success	**Improvement**	**Failure**	**Statistics : P**
Mean FCV (mL) / *SD*	171.4 / 88	139.4 / 84	161.5 / 70	P = 0.90
Mean MCC (mL) / *SD*	286.4 / 128	202.4 / 131	195 / 114	P = 0.12
Mean P det. max. (cm H_2O) / *SD*	61.7 / 20	69 / 26	64 / 22	P = 0.92

made early or late after spinal injury (25). Still MS is a progressive disease, and the duration of the disease is associated with new neurological lesions.

In the present study all of the patients practiced ISC. The induced hypocontractility of the detrusor by the treatment led to urinary retention that often required intermittent self- catheterization (17).

Patients with MS often have an association of NDO and detrusor sphincter dyssynergia, which results in post-void residue. They are at very high risk of urinary retention. Up to 98% of patients with MS require ISC after BTX-A bladder injection (20). This raises the question about witch dosage of BTX-A should be applied. The use of BTX-A treatment in NDO was pioneered by Schurch et al. in 2000 (23). In this study, 200 or 300 U of BTX-A (Botox, Allergan) was used in 19 patients with SCI, who already practiced ISC. The two patients who had a moderate improvement without complete continence had the lower dose of 200 U (23). More recently, Menhert et al. treated 12 patients suffering from MS and NDO, using the dose of 100 U of BTX-A. They showed significant improvement of cystometric and clinical parameters. Post-void residual volume increased, but most patients were able to remain on voluntary voiding. Two patients needed ISC once to twice daily on demand, one patient needed a supra pubic catheter (21). However, all patients in whom BTX-A treatment is planned should be taught ISC (21). Lekka and Lee reported three cases of severely disabled patients who had long term indwelling catheters. These patients were unable to do ISC, and suffered from incontinence despite the indwelling catheter. They were treated with BTX-A bladder injection and suprapubic catheterization. They all became pad-free (26). This management could be an alternative to surgical treatment as ileal cystoplasty.

No relevant complication was noted in the present study. The injections can be complicated with transient pain at the injection site (11), urinary tract infection (2 to 32% of the cases) (14), or haematuria (2 to 21% of the patients) (14). Other side effects of BTX-A injections are rare, such as allergic reaction to the toxin or transient flu. A few cases of generalized muscle weakness after bladder injections have been reported (17) and not observed in our series.

CONCLUSIONS

MS is a neurological central disease with disseminated lesions in time and space. NDO is frequent and causes overactive bladder syndrome with urgency, frequency, and urge incontinence. This alters quality of life. Upper urinary tract complications can occur. Therefore, NDO has to be efficiently treated. Usual medications as anticholinergic agents can fail. Refractory NDO is nowadays usually treated by BTX-A bladder injections.

BTX-A bladder injection therapy was efficient to treat refractory NDO in MS patients, with an overall efficacy of 77%, in terms of clinical and urodynamic results. The efficacy of this treatment was similar to what is observed in patients suffering from SCI.

Still, 23% of the patients showed no improvement of their clinical symptoms and urodynamic parameters. A predictive factor of this bad response to treatment was the duration of MS. Duration of MS is also known to be associated with increased risk of upper urinary tract complications. This is an argument for an early proposal of BTX-A bladder injection therapy for refractory NDO in patients with MS.

CONFLICT OF INTEREST

None declared.

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Comparative study between trimetazidine and ice slush hypothermia in protection against renal ischemia/reperfusion injury in a porcine model

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ABSTRACT

Purpose: The aim of the study was to compare the effects of renal ice slush hypothermia and the use of trimetazidine in the protection against ischemia/reperfusion (I/R) injury.
Materials and Methods: Fifteen farm pigs were submitted to left kidney ischemia and right nephrectomy during the same procedure. Animals were divided into three groups. Group 1 was submitted to warm ischemia; Group 2 was submitted to cold ischemia with ice slush; and Group 3 received trimetazidine 20 mg one day and 4 hours before surgery. Ischemia time was 120 minutes in all three groups. Serum creatinine (SCr) and plasma iohexol clearance (CLioh) were measured before surgery and on postoperative days (PODs) 1,3,7, and 14. Semi-quantitative analyses of histological alterations were performed by a pathologist. A p value of < 0.05 was considered significant.
Results: All groups showed elevation of serum creatinine in the first week. Serum creatinine was higher in Group 3 in the first and third postoperative days (Mean Cr: 5.5 and 8.1 respectively). Group 2 showed a lower increase in creatinine and a lower decrease in iohexol clearance than the others. Renal function stabilized in the fourteenth POD in all three groups. Analyses of histological alterations did not reach statistical significance between groups.
Conclusion: Trimetazidine did not show protection against renal I/R injury in comparison to warm ischemia or hypothermia in a porcine model submitted to 120 minutes of renal ischemia.

Key words: *kidney; ischemia; trimetazine; hypothermia; reperfusion injury*
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INTRODUCTION

Occlusion of the renal artery and vein may be necessary in many situations during urological procedures and is related to renal ischemia/reperfusion (I/R) injury. Such an injury is often related to acute and chronic renal dysfunction (1,2). Renal hypothermia is frequently used to overcome this problem. However, in some occasions hypothermia is not feasible, and renal protection must be accomplished using other mechanisms.

Several drugs have been studied in the protection of the kidney from I/R injury (3-13). The anti-anginal medication trimetazidine (TMZ) has been shown to protect the myocardium cells through inhibition of fatty acid oxidation and reciprocal activation of pyruvate oxidation, resulting in less production and accumulation of lactate and hydrogen cation, H+, during ischaemia (14). Experimental studies have also shown a protective effect in kidney I/R injury (15,16). Nevertheless, there has been no comparative study between renal hypothermia and trimetazidine in the protection of I/R injury.

MATERIALS AND METHODS

The study was performed with the approval of our Institutional Animal Care and Use Committee (CEEA/UNESP) on fifteen farm pigs weighing 12.2 to 21.4 kg.

Surgical procedures

All animals received preoperative intramuscular administration of 1.0 mg/kg xylazine (Divisão Vetbrands Saúde Animal - SP), 0.1 mg/kg acepromazine (Laboratórios Univet S.A. - SP) and 10 mg/kg ketamine (Divisão Vetbrands Saúde Animal - SP). A 22-gauge polyethylene catheter (Becton Dickinson Ind. Cirúrgicas Ltda - MG) was inserted into an ear vein and induction of anesthesia was achieved with 0.25 mg/kg diazepam (Hipolabor Farmacêutica Ltda - MG) and 5 mg/kg ketamine. After endotracheal intubation, isoflurane (Cristália Produtos Químicos Farmacêuticos Ltda - SP) and 100% oxygen were used for anesthesia maintenence. For additional analgesia during the procedure, intravenous 5 μg/kg fentanyl (Hipolabor Farmacêutica Ltda - MG) was used. The surgical procedures were performed under sterile conditions. Animals were positioned in left lateral decubitus and a right nephrectomy was achieved by lumbodorsal incision. After closing the incision, the animal was placed in right lateral decubitus and a left lumbodorsal incision was made to access the left kidney. One hundred twenty- minute ischemia was accomplished by hilar clamping with a Satinsky clamp. A probe placed 0.5 cm deep in the renal cortex constantly measured the renal temperature in a continuous fashion. The internal jugular vein was dissected for blood sampling and drug administration. In the group submitted to renal hypothermia, this was achieved by surrounding the left kidney with a rubber sheet on which sterile ice slush was placed to completely immerse the kidney.

Experimental groups

Fifteen farm pigs were randomized into three groups. Group 1 was submitted to 120 minutes of warm ischemia (WI) without any kind of renal protection. Group 2 was submitted to 120 min. of cold ischemia with ice slush. Group 3 received 20 mg oral trimetazidine, 24 hours and 4 hours before surgery, and was also submitted to 120 min of ischemia. Five animals in each group were followed for 14 days. Two animals in Group 1 and one in Group 3 died and were replaced to complete the follow-up.

Renal function assessment

Renal function was assessed using serial glomerular filtration rate measurements according to plasma iohexol clearance (CLioh) and serum creatinine (SCr) determination. SCr and CLioh were measured before surgery and on postoperative days (PODs) 1,3,7, and 14. Iohexol clearance was measured by one-compartment single sample clearance (17). High Performance Liquid Chromatography (HPLC) was used to measure iohexol plasma concentration as previously reported (18).

Histology

Animals were sacrificed on postoperative day 14 when renal samples were collected for microscopy. Two conventional stains were applied: hematoxylin - eosin (HE) and periodic acid Schiff (PAS) to evaluate proximal tubule brush border integrity. Seven basic morphological patterns (apical cytoplasm vacuolization, tubular necrosis, tubular dilatation, cell detachment, brush border integrity, intracellular edema, denuded basement membrane) typical of proximal tubular injury were graded in 5-point scales as follows: 1, no abnormality; 2, lesions affecting less than 25% of kidney samples; 3, lesions affecting 25-50% of kidney samples; 4, lesions affecting 50-75% of kidney samples, and 5, lesions affecting more than 75% of kidney samples. A pathologist blinded to the experimental conditions analyzed the histological alterations.

Statistical analysis

Statistical analyses were performed using the SPSS software, Version 15.0. For continuous data ANOVA and Kruskal-Wallis were used. Categorical

data were analyzed using the Fisher's exact test. A 0.05 p value was considered statistically significant.

RESULTS

The outcomes from Groups 1 and 3 differed markedly from the group submitted to cold ischemia. Two animals in Group 1 and one animal in Group 3 died because of acute renal failure confirmed by the increase in serum creatinine before the end of the study and were replaced. One animal in Group 3 presented with a retroperitoneal hematoma by the time of sacrifice, but no histological alterations on renal samples were observed.

Renal temperature was kept around 33-34ºC in Groups 1 and 3, and around 16ºC in Group 2. Body temperature remained constant (around 37ºC) in all three groups (Table-1).

All groups showed elevation of serum creatinine values in the first week after the procedure (Figure 1). Serum creatinine values had the lowest increase in Group 2 in the first and third postoperative days (Mean Cr: 2.2 and 1.2 respectively) compared to group 3 (p = 0.005). Comparisons between Groups 1 and 2 and between Groups 1 and 3 did not reach statistical significance in the first and third postoperative days. There was no significant difference between groups after seven days of surgery (Table-2).

Table 1 *- Comparison of weight, renal and body temperature between groups.*

	Warm Isquemia Group 1	**Hypothermia Group 2**	**Trimetazidine Group 3**	
Weight (Kg)	9.11 ± 6.80	8.1 ± 6.36	7.1 ± 1.43	0.845*
Renal temperature (ºC)	33.4 ± 2.26	16.13 ± 2.38	34.09 ± 1.18	< 0.001*
Body temperature (ºC)	37.03 (36.53 ; 39.00)	37.32 (36.93 ; 38.61)	37.65 (37.36 ; 38.09)	0.852(**)

(*) ANOVA independent samples (α = 0.05) GLRes = 12. Summary in mean & SD.
(**) Kruskal-Wallis (α = 0.05). Summary in median & quartile.

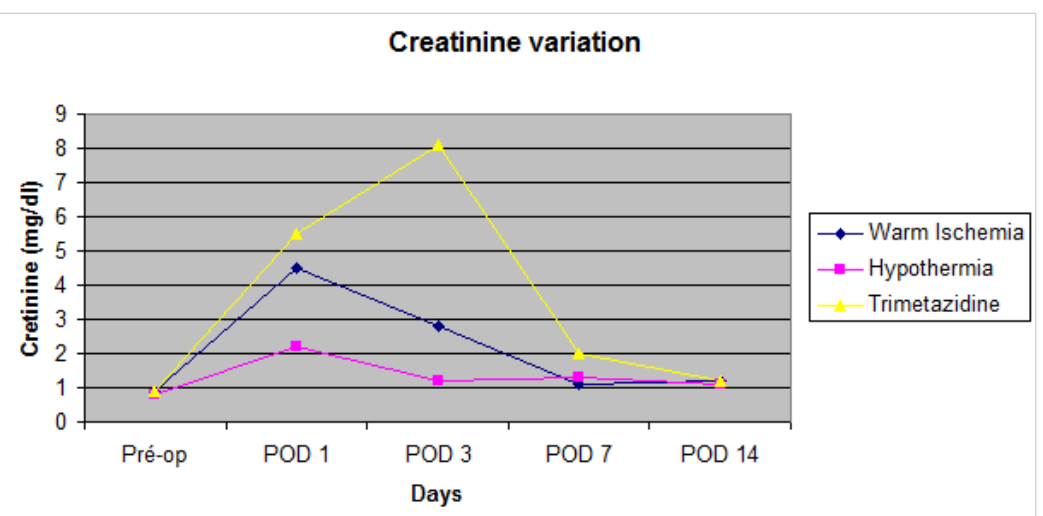

Figure 1. *Increase of creatinine values on POD1, POD3 and return to baseline values on POD14.*

Table 2 *- Creatinine values at baseline and PODs 1, 3, 7 and 14 in each group.*

Moment	Creatinine (mg/dl)			P
	Warm Ischemia Group 1	Hypothermia Group 2	Trimetazidine Group 3	
Pre-op	0.90 (0.75 ; 0.90)	0.80 (0.70 ; 0.85)	0.90 (0.70 ; 0.90)	0.438(**)
POD 1	4.50 (3.45 ; 4.75)	2.20 (2.00 ; 3.20)	5.50 (4.85 ; 6.25)	0.005(**)
POD 3	2.80 (1.75 ; 6.70)	1.20 (1.05 ; 1.35)	8.10 (3.90 ; 9.75)	0.005(**)
POD 7	1.10 (0.70 ; 2.80)	1.30 (1.15 ; 8.35)	2.00 (1.60 ; 9.35)	0.194(**)
POD 14	1.20 (0.95 ; 1.50)	1.10 (1.05 ; 1.40)	1.20 (1.00 ; 2.60)	0.931(**)

(**) Kruskal-Wallis (α = 0.05). Summary in median & quartile.

All groups showed decreased iohexol clearance in all moments assessed after the procedure (Figure 2). Group 2 (hypothermia) showed the lowest decrease in iohexol clearance in the first POD (Table-3) compared to the other two groups. Comparison between Groups 1 and 3 did not reach statistical difference. All groups showed more than 25% decline in iohexol clearance by the end of the follow-up.

Semi-quantitative analyses of histological alterations did not reach statistical difference between groups.

DISCUSSION

Interruption of renal blood flow is often necessary during surgical procedures such as partial nephrectomy, renal transplantation, and vascular surgery. However, vascular clamping is related to increased risk of postoperative complications such as urinary fistula, acute and chronic renal failure, and necessity of temporary dialysis (19). Duration of ischemia is the most important factor related to recovery of renal I/R injury. The historical safe

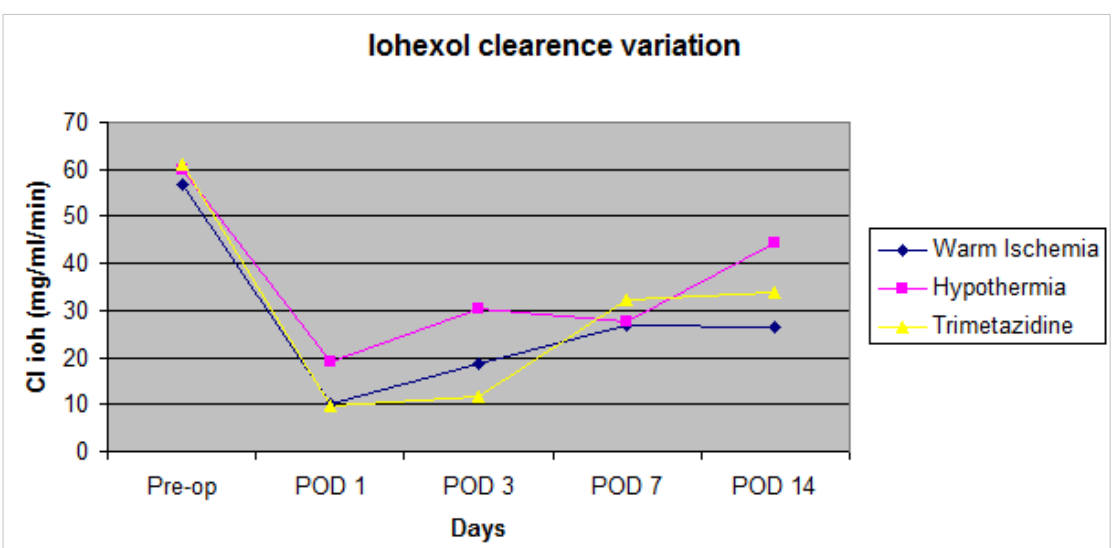

Figure 2. *Decrease of iohexol clearance on POD1 and POD2 with stabilization of the renal function on POD14.*

Table 3 *- Plasma iohexol clearance values at baseline and PODs 1, 3, 7 and 14 in each group.*

Moment	Plasma Iohexol Clearence (mg/ml/min)			p
	Warm Ischemia Group 1	Hypothermia Group 2	Trimetazidine Group 3	
Pre-op	56.6 (46.6 ; 59.1)	59.8 (46.3 ; 63.9)	60.9 (47.6 ; 67.9)	0.595(**)
POD 1	10.1 (7.8 ; 10.9)	19.2 (15.6 ; 29.6)	9.6 (9.3 ; 12.0)	0.009(**)
POD 3	18.8 (10.4 ; 25.4)	30.2 (20.9 ; 31.7)	11.8 (6.9 ; 24.6)	0.125(**)
POD 7	26.9 (12.4 ; 31.1)	27.7 (11.2 ; 36.5)	32.1 (15.1 ; 33.0)	0.827(**)
POD 14	26.6 (17.6 ; 39.0)	44.38 (32.5 ; 46.6)	34.0 (16.0 ; 43.4)	0.357(**)

(**) Kruskal-Wallis ($\alpha = 0.05$). Summary in median & quartile.

duration of warm ischemia time, where full recovery of renal function is expected, is thought to be 30 minutes (20). Based largely on animal models, most studies suggest that warm ischemia longer than 30 minutes results in significant immediate functional loss with either incomplete or absent late recovery (21,22). More recent observations have challenged the maximal safe duration of warm ischemia, suggesting that renal pedicle clamping for 90 minutes is safe in the porcine model (22,23). In our study we have used a 120 minutes ischemia time that is sufficient to cause 25% decline in glomerular filtration rate (24). In those cases where longer ischemia time may be required, adjuvant methods for renal protection are advisable.

One of the most used and effective methods of renal protection is hypothermia. Optimum temperature has been shown to be 15ºC in the canine model (21). Surface cooling of the kidney has been the most popular method of in situ hypothermia and has been accomplished by a variety of techniques such as surrounding the kidney with ice slush, immersing the kidney in a cold material, retrograde ureteral infusion of cold solution, or applying an external cooling device to the kidney (20,25,26). The most popular method has been to surround the mobilized kidney with a rubber sheet on which sterile ice slush is placed to completely immerse the kidney. Surface hypothermia in this manner is technically simple and very effective, and all of the requisite material is readily available in any operating room. Some disadvantages may be related to ice slush hypothermia. The core renal temperature falls slowly, generally taking 15 to 20 minutes to reach the desired level, and renal cooling is often non-homogeneous. Moreover, with the advent of minimally invasive surgery such as laparoscopic partial nephrectomy, hypothermia becomes more difficult to accomplish.

Another approach to in situ renal preservation that does not involve hypothermia is the use of a variety of pharmacologic agents to prevent renal injury. Agents that have been tested fall into four basic categories: diuretic agents, vaso-active drugs, membrane-stabilizing drugs, and agents that act to replenish intracellular levels of ATP. The anti-anginal medication trimetazidine has been shown to increase intracellular ATP levels.

Several papers have shown the protective effect of trimetazidine on kidney grafts from cold preservation and reperfusion (27,28) and against warm ischemia (12,15,16). Hauet et al. (27) evaluated the renal function of isolated perfused pig kidneys after

48 hours of cold storage with Euro-Collins (EC) solution plus trimetazidine (EC+TMZ), standard EC solution, or University of Wisconsin (UW) solution. The author studied the effect of TMZ during cold storage. The addition of TMZ to the EC solution improved the preservation quality and renal tubular function, and gave additional protection from reperfusion injury compared to EC or UW solutions alone. The same investigators studied the effect of TMZ on renal function and lipid peroxidation in an isolated perfused pig kidney (28). Renal function was significantly improved and lipid peroxidation reduced after preservation in Euro-Collins solution plus TMZ. Jayle et al. (12) evaluated the effect of TMZ pretreatment on the injury caused by warm ischemia for 45, 60, and 90 minutes, and reperfusion in a pig kidney model. TMZ pretreatment reduced deleterious effects after 45 minutes and particularly 60 and 90 minutes of WI However, the exact mechanism of action of TMZ on renal tubular cells is not clear.

In our study trimetazidine did not show protective effect on the kidney against I/R injury. When the serum creatinine values were analyzed there was no statistical difference between the warm ischemia (1) and trimetazidine (3) groups. However, creatinine was higher in Group 3 compared to Group 2. When the iohexol clearance was analyzed both the warm ischemia and trimetazidine groups had lower levels of clearance compared to the hypothermia group. However, the differences between the warm ischemia and the trimetazidine group were not so clear.

Some possible limitations of our study may explain these results such as an eventual lower plasmatic concentration achieved by the oral administration of trimetazidine; different metabolic pathways involved in nephron energy production and consumption; or species variability. Although histological alterations were not evident in the kidney of the animal in Group 3 that presented with retroperitoneal hematoma, this surgical complication may have influenced kidney function. However, when this animal was excluded from analyses, the hypothermia group still had a better outcome than the other two groups. Also, none of the previous papers used such a long warm ischemia time (120 minutes) as we did. This may have played a negative impact on our results.

Our results are in contrast to some previous publications that suggested a protective effect of trimetazidine on kidneys submitted to warm ischemia. Larger series with different warm ischemia times are warranted in order to definitely show the exact role of trimetazidine on renal protection to warm ischemia time.

CONCLUSIONS

Trimetazidine did not show protection against renal I/R injury in comparison to warm ischemia or hypothermia in a porcine model submitted to 120 minutes of ischemia.

ABBREVIATIONS

ANOVA - Analysis of variance
ATP - Adenosine triphosphate
CEEA - Comite de ética e experimentação animal
CLioh - Iohexol clearance
EC - Euro-Collins
HPLC - High Performance Liquid Chromatography
I/R - Ischemia/Reperfusion
PODs - Postoperative days
SCr - Serum creatinine
TMZ - trimetazidine
UNESP - Universidade Estadual Paulista
UW - University of Wisconsin solution
WI - warm ischemia

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CONFLICT OF INTEREST

None declared.

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Urethral skip metastasis from cancer penis or a second malignancy? A dilemma!

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A 76-year old man presented with stricture of bulbar urethra for which he underwent urethral dilatation and was advised to perform self urethral dilatation. Four months later he noticed an ulcerative lesion over glans penis and its biopsy revealed a verrucous carcinoma. This was managed by partial penectomy. The resection margins were free of tumor. Two months following surgery, the patient again developed poor urinary stream. Physical examination revealed normal urethral meatus and there was a hard swelling in midperineal area suggestive of urethral calculus. Retrograde urethrogram showed an irregular filling defect in peno-bulbar urethra (Figure-1).

Cystoscopy was inconclusive as only one surface of the lesion was visible and that too was covered by slough. In view of advance age and localized excisable disease, the patient underwent wide excision of the mass with permanent perineal urethrostomy. The histopathological examination of the mass showed hyperkeratinised stratified squamous epithelium showing acanthosis and papillomatosis suggestive of verrucous carcinoma (stage T2).

COMMENTS

He underwent successful management of penile tumor with tumor free margins. Subsequent urethral involvement (skip lesion) in penile cancer is uncommon. It is known that urethral tumors usually arise in areas of urethral stricture (1). Whether this patient developed an independent second malignancy or whether it was a metastasis from penile cancer is debatable as tumors at both these sites are squamous in nature. However, metastasis seems more likely because of the short interval of only 2-months between partial penectomy and the development of the urethral lesion. Some etiologic factors for penile as well as urethral cancers are similar like HPV infection (2). However, we could not find any report of co-association between these two cancers in the literature.

Urethral cancer is an uncommon condition. The presentation is varied and includes urethral bleed, obstructed urinary flow or perineal urethrocutaneous fistula (3). The investigation of choice is controversial although most investigators today believe that MRI is the best imaging modality in these cases (4). We also had a similar experience and found that the MRI images (Figure-2) were much superior to the CT scan. The patient was managed by wide local excision which is standard therapy for localized disease.

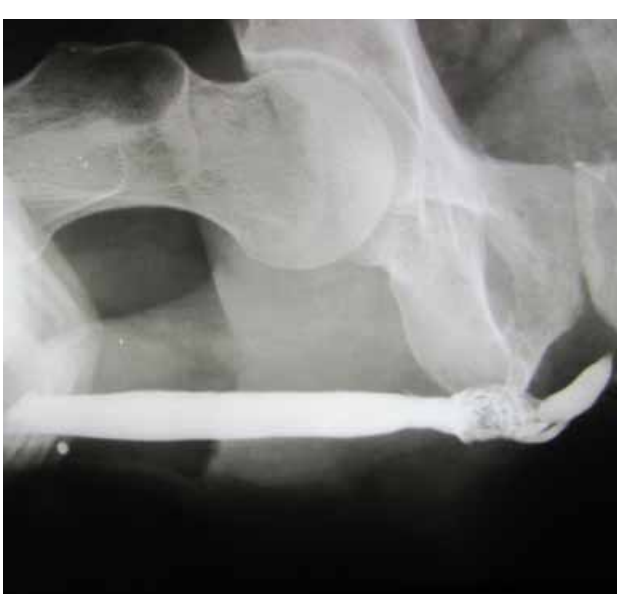

Figure 1 - *Retrograde urethrogram shows irregular contrast filling in the penobulbous urethra.*

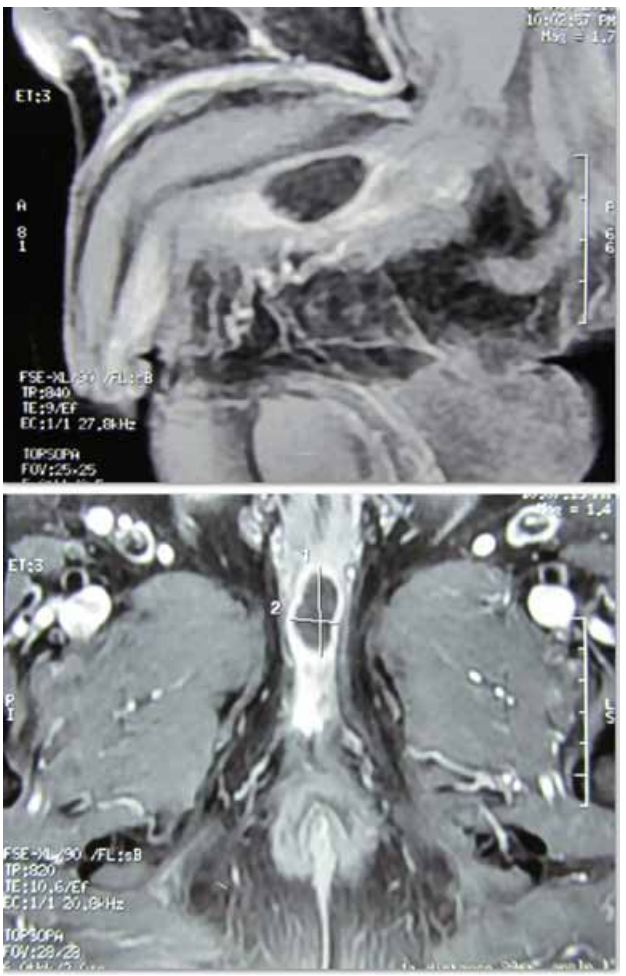

Figure 2 - *MRI urethra shows a lesion displaying heterogenous signal intensity alterations isointense on T1 WIs and hypointense on T2 WIs in peno-bulbous urethra with mild peripheral post-contrast enhancement.*

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UROLOGICAL SURVEY

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STONE DISEASE

Ureteral avulsion during contemporary ureteroscopic stone management: "the scabbard avulsion"

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J Endourol. 2011; 25: 1259-62

Ureteral avulsion during ureteroscopic stone management is extremely rare. To date, many publications reporting avulsion have been associated with "blind basket extraction" under fluoroscopy and the use of the Dormia stone basket. Fortunately, despite the significant rise in the numbers of ureteroscopic cases being performed, the rate of ureteral avulsion remains low. This is likely in part because of improvements in ureteroscope technology and stone manipulation devices. We present three recent cases of ureteral avulsion referred to our center for further management. To our knowledge, these cases represent the first published description of avulsion where the ureteroscope became wedged in the intramural ureter, resulting in full-length avulsion of the ureter. The avulsion occurs both proximally and distally with a resultant length of ureter left attached to the ureteroscope. We dub this mechanism the "scabbard" avulsion. We describe the most likely mechanism of this injury, with suggestions on how to prevent it and how to release the ureteroscope should it become wedged in the intramural ureter.

Editorial Comment

The authors have identified a new mechanism of injury to the ureter during semi-rigid ureteroscopy. The authors propose that excessive upward force on the semi-rigid ureteroscope lead to impaction of the scope in the intramural ureter. Withdrawal of the scope then led to avulsion of the intramural ureter at the bladder, followed by avulsion of the UPJ with further extraction of the scope, leaving the ureteral segment as a "scabbard on a sword". The authors discuss the potential that this complication could occur with the use of larger ureteral access sheaths. They comment that the hydrophilic coating may prevent such an injury. However, it is feasible that if the ureteral access sheath is "tight" on the way up, by the end of a lengthy procedure at which point the hydrophilic coating may no longer be "wet"; significant resistance may be encountered on withdrawal of the sheath. The authors propose that the use of a safety wire may help prevent "impaction" of the scope in the ureter. They propose liberal use of a flexible ureteroscope above the iliac vessels, and lubrication of the proximal shaft of the semi-rigid ureteroscope if plans are to advance it beyone the iliac vessels. The authors also emphasize that excessive upward force with the semi-rigid ureteroscope should be avoided. Lastly, they propose that if an impacted ureteroscope is encountered, one attempt placement of a second endoscope alongside it an utilize a holmium laser to incise the ureteral orifice.

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The clinical research office of the endourological society percutaneous nephrolithotomy global study: staghorn versus nonstaghorn stones

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Purpose: The study compared characteristics and outcomes in patients with staghorn or nonstaghorn stones who were treated with percutaneous nephrolithotomy (PCNL) within the Clinical Research Office of the Endourological Society (CROES) PCNL Global Study.
Patients and Methods: Data over a 1-year period from consecutively treated patients from 96 centers worldwide were collated. The following variables in patients with staghorn or nonstaghorn stones were compared: National prevalence, patient characteristics, access method, puncture frequency and outcomes, including bleeding rates, operative time, and duration of hospital stay.
Results: Data from 5335 eligible patients were collated; 1466 (27.5%) with staghorn and 3869 (72.5%) with nonstaghorn stones. Staghorn stone presentation varied between centers from 67% in Thailand to 13% in Argentina. The frequencies of previous procedures were similar between groups, but shockwave lithotripsy was less frequent in patients with staghorn stones compared with nonstaghorn (16.8% vs 22.6%) and positive preoperative urine cultures were more frequent in patients with staghorn than nonstaghorn stones (23.4% vs 13.1%). Patients with staghorn stones underwent multiple punctures more frequently than those with nonstaghorn stones (16.9% vs 5.0%). Postoperative fever, bleeding, and the need for blood transfusion were more frequent, the median operative time and duration of hospital stay were longer, while the proportion of patients remaining stone free was lower (56.9% vs 82.5%) in patients with staghorn than nonstaghorn stones.
Conclusions: The proportion of patients with staghorn stones varies widely between centers. Stone-free rates were lower, complications more frequent, and operative time and hospital stay were longer in patients with staghorn stones.

Editorial Comment

The findings of this study are not unexpected; staghorn calculi present a unique challenge to the endourologist; with anticipated higher rates of complications and lower rates of success. However, the study demonstrates clearly that though the rates of complications were higher and hospital stay and OR times longer, they were not prohibitively so; PCNL remains a high standard of care for staghorn calculi. The information provided is useful for counseling patients on the contemporary risks of PCNL and the anticipated success and recuperation. Though the authors report that staghorn calculi are more common in women and have a higher rate of positive urine cultures, they did not report the stone analyses on these patients. It would be useful to evaluate whether the risk of infectious complications is higher in patients with struvite calculi. The relatively low utilization of multiple accesses for staghorn calculi alludes to a high utilization of flexible endoscopes and adjunctive procedures such as flexible ureteroscopy and SWL. The authors do not report the percentage of patients who indeed underwent these procedures. Advocates of the multiple access approach would likely conclude that the low stone free rate of 57% could have been improved had multiple accesses been employed.

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ENDOUROLOGY & LAPAROSCOPY

Laparoendoscopic Single-site Surgery in Urology: Worldwide Multi-institutional Analysis of 1076 Cases
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Background: Laparoendoscopic single-site surgery (LESS) has gained popularity in urology over the last few years.
Objective: To report a large multi-institutional worldwide series of LESS in urology.
Design, Setting, And Participants: Consecutive cases of LESS done between August 2007 and November 2010 at 18 participating institutions were included in this retrospective analysis.
Intervention: Each group performed a variety of LESS procedures according to its own protocols, entry criteria, and techniques.
Measurements: Demographic data, main perioperative outcome parameters, and information related to the surgical technique were gathered and analyzed. Conversions to reduced-port laparoscopy, conventional laparoscopy, or open surgery were evaluated, as were intraoperative and postoperative complications.
Results and Limitations: Overall, 1076 patients were included in the analysis. The most common procedures were extirpative or ablative operations in the upper urinary tract. The da Vinci robot was used to operate on 143 patients (13%). A single-port technique was most commonly used and the umbilicus represented the most common access site. Overall, operative time was 160 ± 93 min. and estimated blood loss was 148 ± 234 mL. Skin incision length at closure was 3.5 ± 1.5cm. Mean hospital stay was 3.6 ± 2.7 d with a visual analog pain score at discharge of 1.5 ± 1.4. An additional port was used in 23% of cases. The overall conversion rate was 20.8%; 15.8% of patients were converted to reduced-port laparoscopy, 4% to conventional laparoscopy/robotic surgery, and 1% to open surgery. The intraoperative complication rate was 3.3%. Postoperative complications, mostly low grade, were encountered in 9.5% of cases.
Conclusions: This study provides a global view of the evolution of LESS in the field of minimally invasive urologic surgery. A broad range of procedures have been effectively performed, primarily in the academic setting, within diverse health care systems around the world. Since LESS is performed by experienced laparoscopic surgeons, the risk of complications remains low when stringent patient-selection criteria are applied.

Editorial Comment

Laparoendoscopic Single-site Surgery in Urology has evolved and this manuscript demonstrates the fast pace of implementation of this new minimally invasive surgical technique worldwide.

A total of 1076 patients were included in the analysis between August 2007 and November 2010 at 18 participating institutions. Different ports and instrumentations were used but the common theme seems to be the evolution of surgical technique and experience of urological laparoscopists that can perform these procedures.

Overall operative time was 160 ± 93 min and estimated blood loss was 148 ± 234 ml. Skin incision length at closure was 3.5 ± 1.5 cm. Mean hospital stay was 3.6 ± 2.7 d with a pain VAS at discharge of 1.5 ± 1.4.

A single-port technique was chosen in 77% of cases and the umbilicus was the predominant site of access (71% of cases). In cases in which a single-port platform was used, 46% involved a homemade device and 54% used a commercially available device. An additional port was used in 23% of cases. In 34% of these, a 2- to 3-mm extra port was used, whereas in the remaining 66% of cases, an extra 5- to 12-

mm additional port was required. The overall conversion rate was 20.8%, with 15.8% of cases converting to reduced-port laparoscopy, 4% to conventional laparoscopy or robotic surgery, and 1% to open surgery. Reasons for conversion were difficult dissection (37% of converted cases), failure to progress (21%), bleeding (25%), difficult suturing (11%), difficult retraction (3%), and difficult access (3%).

The intraoperative complication rate was 3.3%, with need for conversion to open surgery occurring in three cases and laparoscopy in five cases.

As the authors concluded the Outcomes demonstrate that a broad range of procedures can be effectively and safely done by applying different LESS techniques in a variety of hospital settings. Undeniably, a solid laparoscopic surgical background and stringent patient-selection criteria are critical for successful LESS.

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Contemporary trends in nephrectomy for renal cell carcinoma in the United States: results from a population based cohort

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Purpose: Despite benefits in functional renal outcome and the similar oncological efficacy of partial nephrectomy for renal cell carcinoma, previous studies show marked underuse of partial nephrectomy. We describe national trends in partial and radical nephrectomy using a contemporary, population based cohort.
Materials and Methods: Using the 2003 to 2008 Nationwide Inpatient Sample we identified 188,702 patients treated with partial or radical nephrectomy for renal cell carcinoma at a total of 1,755 hospitals. Multivariate logistic regression was used to assess the independent associations of patient and hospital characteristics with partial nephrectomy. Post-estimations from multivariate logistic regression were done to ascertain the annual predicted probability of partial nephrectomy by hospital feature.
Results: Overall 149,636 (79.3%) and 39,066 patients (20.7%) underwent radical and partial nephrectomy for renal cell carcinoma, respectively. Partial nephrectomy use increased each year from 16.8% in 2003 to 25.1% in 2008 (p for trend <0.001). On multivariate analysis patients were more likely to undergo partial nephrectomy at teaching (OR 1.31, $p < 0.001$) and urban (OR 1.13, $p = 0.05$) hospitals compared to nonteaching and rural hospitals, respectively. Each quartile of higher nephrectomy annual volume was associated with higher odds of partial nephrectomy compared to the lowest quartile (OR 1.21, $p < 0.001$). Although annual predicted partial nephrectomy use increased across all hospitals, differences in annual partial nephrectomy use by teaching status, site (urban vs rural) and case volume persisted with time.
Conclusions: Although the use of partial nephrectomy for renal cell carcinoma is increasing nationally across all hospitals, academic and urban hospitals as well as those with higher nephrectomy volume continue to show higher partial nephrectomy use for renal cell carcinoma.

Editorial Comment

Since development of laparoscopy in urology, we evolved from open nephrectomy to partial open nephrectomy to Laparoscopic radical Nephrectomy, then nephron-sparing laparoscopic partial nephrectomy

and currently ablative technique. This study demonstrates a national increase in the use of PN as an acceptable surgical option for RCC. While the annualized rate of PN per 100,000 individuals increased by 90% from 2003 to 2008, there was a corresponding 49% increase for PN and a 10% decrease for RN as a proportion of all renal surgeries for RCC in our study. Prior epidemiological studies from SEER (Surveillance, Epidemiology and End Results) and the National Kidney Cancer Database have shown marked underuse of PN for small renal masses, which was further supported by other studies using the NIS from 1998 to 2002.

This study suggests that there continues to be a gradual increase in PN use for RCC nationwide. While PN was more likely to be done at hospitals with a higher surgical volume, urban setting and teaching status from 2003 to 2008, the annual rate of increase was similar at hospitals previously identified with PN underuse. Low case volume, nonteaching and rural hospitals continued to have gradual increases in annual predicted PN use with time.

The difficult and steep learning curve to learn laparoscopic partial nephrectomy may direct training towards ablative small renal masses techniques to address some of the issues, since the oncological outcomes seem comparable to other nephron-sparing techniques.

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IMAGING

Distal ureteral calculi: US follow-up

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Purpose: To assess accuracy of ultrasonographic (US) follow-up of distal ureteral calculi by using computed tomography (CT) and conventional radiography (kidneys, ureters, and bladder) as reference standards.
Materials and Methods: The study was approved by the Regional Ethics Committee, and written informed consent was obtained. One hundred fifty-eight patients with CT-diagnosed symptomatic ureteral calculi, for whom follow-up imaging was ordered, were enrolled from February 2006 to December 2008. Six were excluded, having not met study entry criteria, with 121 men (mean age, 49 years; range, 20-91 years) and 31 women (mean age, 44 years; range, 34-77 years) completing the protocol with adequate reference standard imaging. Targeted transabdominal US occurred coincidently with follow-up CT (n = 92) or radiography (n = 60), with US evaluation prospectively compared considering sensitivity and specificity. Statistical analysis was performed with a $\chi(2)$ test, t test, or paired t test, as appropriate.
Results: Results of nine US examinations were nondiagnostic because of inadequate ureteral visualization, and among these, two cases showed residual distal calculi. Of the remaining 143 patients, 33 had residual distal calculi, all visualized with US. There was a single false-positive study, giving sensitivity, including nondiagnostic US examinations, of 94.3% (95% confidence interval [CI]: 80.8%, 99.3%) and specificity of 99.1% (95% CI: 95.3%, 100%). All calculi appeared hyperechoic with posterior acoustic shadowing. Additional diagnostic features included presence of a hypoechoic rim and Doppler twinkle artifact. Mean stone length was 7.2 mm ± 2.6 (stan-

dard deviation) (range, 4-18 mm). Mean ureteral length visualized was 36.4 mm (range, 12-77 mm), with calculi positioned at a mean of 13.1 mm ± 11.2 (range, 0-40 mm) from the ureterovesical junction (UVJ). Nondiagnostic results were more likely with bladder volume of 110 mL or less (eight [16%] of 50 vs one [1%] of 102, P = .0009). Conclusion: Ureteral calculi within 35 mm of the UVJ can be accurately followed-up by using transabdominal US, which substantially reduces patient radiation burden.

Editorial Comment

Using non-contrast CT for follow-up urinary tract stone is of concern because this entity commonly occurs in a relatively young population. Recently low radiation dose CT protocol has been developed for urinary tract follow-up. The effective radiation dose to the patient range from 8-10 mSv for the standard non-contrast CT protocol, from 3-5 mSv for low dose CT-protocol and from 0.5-1.2 mSv for conventional plain film of the abdomen.

This is a retrospective study that shows that in patients with impacted ureteral stone demonstrated by previous CT, US alone can be of value for the patients' follow-up allowing the detection of residual distal ureteral stone. US showed high sensitivity and specificity when compared with non-contrast CT and conventional abdominal plain film. Calculi within 35 mm of the ureterovesical junction, larger than 4 mm (mean length of residual calculi = 7.2 mm) were better detected in non-obese patients with adequate bladder distension (150-200 mL).

Ultrasound (US) is a noninvasive, safe technique, which can detect acute urinary obstruction due to ureteral stone. Since it is an operator dependent technique and much of ureteral length is frequently obscured by bowel gas its accuracy for detecting ureteral stones varies from 4-83%. Color Doppler sonography is useful as a complimentary when the presence ureteral stone is associated with a specific artifact called "twinkle artifact". Abnormal ureteral jetting is another useful Color Doppler finding for the characterization of distal ureteral stone. In obese, dehydrated patients or in patients presenting an empty bladder, transvaginal or transrectal ultrasound could be also a useful complimentary approach for the detection of distal ureteral stone.

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Evaluation of upper urinary tract tumors with portal venous phase MDCT: a case-control study

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Objective: The purpose of this article is to assess the detection and negative prediction rate of upper urinary tract tumors in nonopacified urinary tracts on portal venous phase MDCT.
Materials and Methods: This retrospective case-control study included 20 patients with upper urinary tract tumors and 40 age- and sex-matched control subjects. All studies were assessed independently by two reviewers. Reviewers determined whether each of four segments of the upper urinary tract could be fully visualized

and whether tumor was present or absent. For each tumor, reviewers characterized its morphologic features (i.e., infiltrative or polypoid mass, urothelial thickening, and associated hydroureter or hydronephrosis).
Results: The detection rate of the proximal two upper urinary tract segments was significantly higher than that for the distal segments ($p < 0.001$). For each upper urinary tract, the sensitivity, specificity, and negative predictive value of portal venous phase MDCT for detecting tumors were 95%, 97%, and 100%, respectively. The positive predictive value for an estimated population prevalence of 0.0005-0.004 was 0.6-4.8%. The morphologic features significant for the presence of tumor were urothelial thickening and the presence of a discrete polypoid mass. Interobserver agreement for all features was good or very good, except for moderate agreement on urothelial thickening involving the ureter ($\kappa = 0.60$).
Conclusion: The detection rate of upper urinary tract tumors on nonopacified portal venous phase is high. Furthermore, in the absence of morphologic features suggestive of urothelial malignancy, a normal-appearing ureter may be reassuring.

Editorial Comment

Three-phase multidetector computed tomography urography (MDCTU) has become the method of choice for investigation patients with hematuria. Three-phase MDCT represents a complete protocol including non-contrast (through abdomen and pelvis), nephrographic/portal (through the kidneys) and excretory phases (through abdomen and pelvis). Such complete protocol is necessary when searching all possible causes of hematuria: calculi, vascular, parenchymal or urothelial abnormalities. In patients with ureteral obstruction, delayed contrast excretion by the kidney preclude contrast opacification of the ureter and sometimes the excretory phase has to be postponed or even repeated. The total amount of effective radiation dose delivered to the patients when using this three-phase protocol varies from 15-18 mSv.

The authors of this retrospective case-control study suggests that nephrographic/portal venous phase MDCT-urography obtained at 70-90 seconds after intravenous injection of contrast material has high PPV and NPV for detecting tumor in the upper urinary tract with an overall sensitivity, specificity, and NPV of 95%, 97%, and 100%, respectively. Another authors' suggestion is that of even when nonopacified, the likelihood of malignancy in a normal-appearing ureter is low and the identification rate of upper urinary tract tumors will still be high.

Any attempt to reduce the total amount of radiation in MDCT-urography should be incentivized but some points of this report deserve some comments. Since in nephrographic phase only both kidneys are imaged, consequently only the pelvocalyceal system and upper portion of the ureter is evaluated. As pointed out by the authors the mid and distal portions of ureter will not be imaged. In our institution we obtain a complete abdominal/pelvic acquisition during portal/nephrographic phase only in patients presenting hydronephrosis and hydroureter on non-contrast phase. In such situation all the urothelial surface is evaluated and urothelial cancer is readily detected. Excretory phase however is still necessary to image contralateral excretory unit due to eventual multifocal tumor, but there is no need for further delayed abdominal/pelvic acquisition(s).

Additionally, in our experience, the absence of abnormalities in the portal phase of a normal-appearing ureter does not always mean absence of tumor. Occasionally small urothelial lesions can be overlooked in nephrographic phase and be retrospectively identified based on findings of the excretory phase.

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PATHOLOGY

Gleason score 7 prostate cancer on needle biopsy: relation of primary pattern 3 or 4 to pathological stage and progression after radical prostatectomy

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J Urol. 2011; 186: 1286-90

Purpose: There have been only a few contradictory publications assessing whether Gleason score 4 + 3 = 7 has a worse prognosis than 3 + 4 = 7 on biopsy material in predicting pathological stage and biochemical recurrence. Older studies predated the use of the modified Gleason grading system established in 2005.
Materials and Methods: We retrospectively studied 1,791 cases of Gleason score 7 on prostatic biopsy to determine whether the breakdown of Gleason score 7 into 3 + 4 vs 4 + 3 has prognostic significance in the modern era.
Results: There was no difference in patient age, preoperative serum prostate specific antigen, maximum tumor percent per core or the number of positive cores between Gleason score 3 + 4 = 7 and Gleason score 4 + 3 = 7. Gleason score 4 + 3 = 7 showed an overall correlation with pathological stage (organ confined, focal extraprostatic extension, nonfocal extraprostatic extension, seminal vesicle invasion/lymph node metastases, $p = 0.005$). On multivariate analysis Gleason score 4 + 3 = 7 ($p = 0.03$), number of positive cores ($p = 0.002$), maximum percent of cancer per core ($p = 0.006$) and preoperative serum prostate specific antigen ($p = 0.03$) all correlated with pathological stage. Gleason score 4 + 3 = 7 on biopsy was also associated with an increased risk of biochemical progression after radical prostatectomy ($p = 0.0001$). On multivariate analysis Gleason score 4 + 3 = 7 ($p = 0.001$), maximum percent of cancer per core ($p < 0.0001$) and preoperative serum prostate specific antigen ($p < 0.0001$) but not number of positive cores correlated with the risk of biochemical progression after radical prostatectomy.
Conclusions: Our study further demonstrates that Gleason score 7 should not be considered a homogenous group for the purposes of disease management and prognosis.

Editorial Comment

The importance of grading prostate carcinoma is evidenced by the fact that it is included in all nomograms used to predict pathologic stage and biochemical progression following radical prostatectomy. The Gleason score may be used to define prognostic groups.

The most frequent combination of Gleason scores defining prognostic groups is 2-4, 5-6, 7, and 8-10. Gleason score 7 may result from 3+4 or 4+3 patterns. There is conflicting data as to the prognostic difference of Gleason score 7 on a biopsy depending on whether the primary pattern is 3 or 4 (1,2).

The study from the Johns Hopkins based on a very large number of patients showed that Gleason score 7 should not be considered a homogeneous group for the purpose of disease management and prognosis.

There was no difference in patient age, preoperative serum prostate specific antigen, maximum tumor percent per core or the number of positive cores between Gleason score 3 + 4 = 7 and Gleason score 4 + 3 = 7. However, Gleason score 4+3=7 showed a statistically significant correlation with pathological stage, and on multivariate analysis an increased risk for biochemical progression following radical prostatectomy.

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Should intervening benign tissue be included in the measurement of discontinuous foci of cancer on prostate needle biopsy? Correlation with radical prostatectomy findings

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Currently, there is no consensus as to the optimal method for measuring tumor length or percentage of cancer on a core when there are 2 or more foci of prostate cancer in a single core separated by benign intervening stroma. One option is to measure discontinuous foci of cancer as if they were 1 single continuous focus. The other option is to add the measurements of the individual separate foci of cancer, ignoring the extent of the intervening benign prostate tissue. The surgical pathology database at The Johns Hopkins Hospital was searched for outside consult cases of prostate needle biopsies reviewed between 2005 and 2010 when the patient came to our institution for radical prostatectomy (RP). Cases were restricted to those with biopsy Gleason score 6 in which there was at least 15% discordance between the outside and our institution in terms of the reported highest percentage of cancer per core per case. One hundred and nine patients were identified fulfiling our inclusion criteria. Seventy-nine showed the same Gleason score in the RP, and 30 had an upgrade to Gleason $\geq$ 7. Including all cases (scores 6, 7, and 8 at RP), there was no significant association between the maximum percentage of cancer per core with organ-confined disease or risk of positive surgical margins, regardless if the cores were measured at Hopkins or at the outside institutions. For cases with no upgrade at RP, the differences between the maximum percentage of cancer per core per case recorded at Hopkins and the outside institutions ranged from 15% to 80%, in which the mean and median differences were 35% and 30%, respectively. The maximum percentages of tumor involvement on a core per case given at our institution more strongly correlated with the presence of organ-confined disease ($P = 0.004$) compared with the percentages given at the outside institutions ($P = 0.027$). Surgical margin positivity was also associated with the maximum percentages of tumor involvement per core given at our institution ($P = 0.004$), whereas the outside percentages were not significant predictors of margin status ($P = 0.2$). In a multivariable analysis, maximum percentage of cancer per core per case measured at Hopkins which includes intervening benign prostate tissue in the measurement was also more predictive of stage and margins than ignoring intervening benign tissue. In summary, our study demonstrated

that for prostate cancer in which the needle biopsy grade is representative of the entire tumor, quantifying cancer extent on biopsy by measuring discontinuous cancer on biopsy from one end to the other as opposed to "collapsing" the cancer by subtracting out the intervening benign prostate tissue correlates better with organ-confined disease and risk of positive margins.

Editorial Comment

The article discusses how to measure on a needle biopsy the linear extent of 2 discontinuous foci of tumor. One option is to measure discontinuous foci of cancer as if they were 1 single continuous focus. The other option is to add the measurements of the individual separate foci of cancer, ignoring the extent of the intervening benign prostate tissue.

The study from Johns Hopkins demonstrated that for prostate cancer in which the needle biopsy grade is representative of the entire tumor, quantifying cancer extent on biopsy by measuring discontinuous cancer on biopsy from one end to the other as opposed to "collapsing" the cancer by subtracting out the intervening benign prostate tissue correlates better with organ-confined disease and risk of positive margins.

There is no consensus among pathologists on this issue. How to measure 2 distinct foci of tumor on a needle biopsy may have implications whenever applying criteria for insignificant cancer (1). For example: in a particular case with only one core showing 2 distinct foci of tumor each one at the very end of the core the resultant percentage of involvement may differ according to the option used for the measurement. Opting to measure the 2 foci of cancer as if they were 1 single continuous focus the percentage of involvement may be more than 50% therefore without criteria for insignificant cancer; opting to add the measurements of the individual separate foci of cancer, ignoring the extent of the intervening benign prostate tissue, the percentage of involvement may be only 10% therefore with criteria for insignificant cancer.

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RECONSTRUCTIVE UROLOGY

Changes in uroflowmetry maximum flow rates after urethral reconstructive surgery as a means to predict for stricture recurrence

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Purpose: A reliable, noninvasive screening method for urethral stricture recurrence after urethroplasty is needed. We hypothesized that changes in flow rates on uroflowmetry relative to preoperative values might help predict stricture recurrence.

Materials and Methods: All men who underwent urethral reconstructive surgery from 2000 to 2009 with adequate preoperative and postoperative uroflowmetry studies were included in the study. Preoperative and

postoperative maximum flow rates were compared. The absolute change in maximum flow rate was compared between patients with and those without recurrence as determined by retrograde urethrogram.
Results: A total of 125 patients treated with urethroplasty were included in the study. Mean ± SD preoperative maximum flow rate was 11.8 ± 9.1 mL per second, which did not vary by stricture length ($p = 0.11$), patient age ($p = 0.46$) or stricture location ($p = 0.58$). The change in maximum flow rate in men without recurrence was 19.2 ± 11.7 vs 0.2 ± 6.4 mL per second ($p < 0.001$) in failed repairs. Setting a change in maximum flow rate of less than 10 ml per second as a screen for stricture recurrence would have resulted in a test sensitivity and specificity of 92% and 78%, respectively. There were 85 men without stricture recurrence who underwent more than 1 postoperative uroflowmetry study. Repeated maximum flow rate values achieved reasonable test reproducibility ($r = 0.52$), further supporting the use of uroflowmetry.
Conclusions: Change in flow rate after urethral reconstruction represents a promising metric to screen for stricture recurrence that is noninvasive and has a high sensitivity.

Editorial Comment

This is a follow-up study to one published a year earlier by the same group (1). In this series of manuscripts they strive to identify a sensitive non-invasive screening test for urethral stricture recurrence after urethroplasty. Follow-up mechanisms after urethroplasty are varied and may include uroflowmetry, symptom assessment with validated instruments, urethrogram or cystoscopy. Herein, the authors present a mechanism to avoid more invasive tests (urethrogram and cystoscopy) in the majority of patients. If one only performs invasive testing on those with a post-operative maximum urinary flow rate that is < 10 cc/s better than their pre-operative maximum flow rate then one will capture 92% of stricture recurrences. In other words, the false negative rate was low. The description of limitations in the discussion is well done and includes mention of the fact that the recurrence rate in this population was slightly high (26%) and that this will artificially increase the positive predictive value; however, for a screening tool, the high sensitivity is the most important attribute.

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Central role of Boari bladder flap and downward nephropexy in upper ureteral reconstruction

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Purpose: We defined the role of the Boari bladder flap procedure with or without downward nephropexy for proximal vs distal ureteral strictures.
Materials and Methods: We retrospectively reviewed the records of all patients who underwent open ureteral reconstruction for refractory ureteral strictures, as done by a single surgeon between 2007 and 2010. Patients were grouped by stricture site into group 1--proximal third of the ureter and group 2--distal two-thirds. Operative techniques and outcomes were reviewed.

Results: During the 30-month study period a total of 29 ureteral reconstruction procedures were performed on 27 patients. A Boari bladder flap was used in 10 of the 12 patients (83%) in group 1 and 10 of the 17 (59%) in group 2. Concomitant downward nephropexy was done more commonly in group 1 (58% vs 12%, p = 0.014). At a mean followup of 11.4 months there was no difference in the overall failure rate between groups 1 and 2 (17% vs 12%). Complications developed more frequently in group 1 (75% vs 35%, p = 0.060), hospital stay was longer (mean 8.0 vs 4.4 days, p = 0.017) and mean estimated blood loss was greater (447 vs 224 ml, p = 0.008).
Conclusions: The Boari bladder flap procedure is a reliable technique to reconstruct ureteral strictures regardless of site. Renal mobilization with downward nephropexy is a useful adjunctive maneuver for proximal strictures.

Editorial Comment

The authors review their experience with reconstruction of ureteral defects. 20 of these patients underwent Boari flap reconstruction with or without downward nephropexy. The focus of the paper is on the utility of Boari flap for reconstruction of upper segment strictures not amenable to ureteroureterostomy. Many urologists avoid Boari flap in such cases due to a fear that the flap will not reach or a concern that is the flap reaches, its length:base width ratio will exceed 3:1. The authors demonstrate that with liberal use of downward nephropexy (used in 7 of 10 upper ureteral Boari flaps) good success rates can be achieved. Of note, no long-term imaging was done unless warranted by recurrent symptoms. So, the risk of long-term silent hydronephrosis due to recurrent obstruction is unclear. There are many ways to anastomose the ureter to the Boari flap. Morey anastomoses the ureter to the flap in an end-to end fashion. I have typically done an end-to-side anastomosis of the ureter into the posterior wall of the flap, typically 2 cm below the upper terminus of the flap. I do this because I feel the blood supply is better than at the tip of the flap and because. I like to reimplant far from the anterior suture line on the bladder flap. The downside of this approach is that I sacrifice a couple of centimeters in length. Based on Morey's results, the end-to-end technique appears to be a good option when the length does not allow an end-to-side anastomosis.

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UROLOGICAL ONCOLOGY

The EORTC tables overestimate the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin: external validation of the EORTC risk tables

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Background: European Organization for Research and Treatment of Cancer (EORTC) risk tables only included 171 patients treated with bacillus Calmette-Guérin (BCG) for non-muscle-invasive bladder cancer (NMIBC).

Objective: To evaluate the external validity of the EORTC tables in patients with NMIBC treated with BCG over 5-6 mo.
Design, Setting, and Participants: Data on 1062 patients treated with BCG were analyzed.
Measurements: Discrimination was assessed using the concordance index (c-index) and the prognostic separation index (PSEP). For calibration, probabilities of recurrence and progression obtained with the EORTC risk tables in our series were compared with those reported by the EORTC.
Results and Limitations: With respect to the discriminative ability of the EORTC model, c-index was similar to those reported in the EORTC series for recurrence. However, c-indices for progression in our series were lower than c-indices reported by Sylvester et al. [1]. Although PSEP in our series was lower than in the EORTC series for recurrence at 1 yr, similar results were found at 5 yr. Regarding progression, PSEP in our series was lower than in the EORTC series. Whilst a successful stratification of recurrence and progression probability at 1 and 5 yr was achieved using the EORTC tables in our series, model calibration showed lower risks of recurrence than those reported by Sylvester et al. [1] in all groups. For progression, lower risks were found in higher-risk groups. There are some limitations in the present study. A different distribution of patients was found, with higher proportions of primary grade 3 T1 tumors and tumors in situ than in the EORTC series. An additional limitation is that prior recurrence of the EORTC table was not included in our parameters. Consequently, two separate analyses were performed for recurrence.
Conclusions: The EORTC model successfully stratified recurrence and progression risks in our cohort. However, the discriminative ability of the EORTC tables decreased in our patients for progression. Moreover, these tables overestimated risks of recurrence and progression after BCG therapy.

Editorial Comment

EORTC risk tables and the related calculator at http://www.eortc.be/tools/bladdercalculator are widely used tools to estimate the risk of recurrence and progression in patients with non-muscle invasive bladder cancer (NMIBC). The underlying database consists on EORTC trials on NMIBC mostly on intravesical chemotherapy before the era of BCG. Therefore, an external evaluation in a different population, and, ideally, with more modern therapy such as BCG, was highly desirable. The CUETO group from Spain evaluated these risk tables in a cohort of patients from 4 own trials, all using BCG. Several conclusions can be drawn from this external validation of the EORTC risk tables. First, the risk tables can be used to assess recurrence and progression in different populations. Second, and even more important to my opinion, the EORTC models overestimated the risk of recurrence and on progression in comparison the real-life CUETO data using BCG therapy, meaning that the Spanish population treated with BCG fared better than the European population mostly treated with intravesical chemotherapy. This can be indirectly be interpreted as a large-population based proof of the success of BCG therapy against recurrence and against progression in high-risk patients.

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Compliance with guidelines for patients with bladder cancer: Variation in the Delivery of Care

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Background: Clinical practice guidelines for the management of patients with bladder cancer encompass strategies that minimize morbidity and improve survival. In the current study, the authors sought to characterize practice patterns in patients with high-grade non-muscle-invasive bladder cancer in relation to established guidelines.

Methods: Surveillance, Epidemiology and End Results (SEER)-Medicare-linked data were used to identify subjects diagnosed with high-grade non-muscle-invasive bladder cancer between 1992 and 2002 who survived at least 2 years without undergoing definitive treatment (n = 4545). The authors used mixed-effects modeling to estimate the association and partitioned variation of patient sociodemographic, tumor, and provider characteristics with compliance measures.

Results: Of the 4545 subjects analyzed, only 1 received all the recommended measures. Approximately 42% of physicians have not performed at least 1 cystoscopy, 1 cytology, and 1 instillation of immunotherapy for a single patient nested within their practice during the initial 2-year period after diagnosis. After 1997, only use of radiographic imaging (odds ratio [OR], 1.19; 95% confidence interval [95% CI], 1.03-1.37) and instillation of immunotherapy (OR, 1.67; 95% CI, 1.39-2.01) were found to be significantly increased. Surgeon-attributable variation for individual guideline measures (cystoscopy, 25%; cytology, 59%; radiographic imaging, 10%; intravesical chemotherapy, 45%; and intravesical immunotherapy, 26%) contributes to this low compliance rate.

Conclusions: There is marked underuse of guideline-recommended care in this potentially curable cohort. Unexplained provider-level factors significantly contribute to this low compliance rate. Future studies that identify barriers and modulators of provider-level adoption of guidelines are critical to improving care for patients with bladder cancer.

Editorial Comment

From a scientific standpoint, guidelines are an evidence-based distillate of the current knowledge on a given disease. So, ideally, every urologist should adhere to at least one guideline and should treat his/her patients accordingly.

This view is over-idealistic indeed, as shown by this paper from Chamie and colleagues. Using SEER data, they showed that only 1 (!) of 4545 patients analyzed received all recommended measures. There was at least a significant improvement over time with regard to BCG treatment.

This study retrospectively assessed treatments until 2002. Further analyses on the developments in the years thereafter, when guidelines really came into everyday's practice, would be highly interesting.

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Detection and clinical outcome of urinary bladder cancer with 5-aminolevulinic acid-induced fluorescence cystoscopy: A multicenter randomized, double-blind, placebo-controlled trial

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Cancer. 2011 Mar 1;117(5):938-47. doi: 10.1002/cncr.25523. Epub 2010 Nov 8.

Background: The medical community lacks results from prospective controlled multicenter studies of the diagnostic efficacy of 5-aminolevulinic acid (5-ALA) cystoscopy on tumor recurrence in patients with superficial bladder tumors.

Methods: A prospective randomized, double-blind, placebo-controlled study was conducted in 370 patients with nonmuscle-invasive urinary bladder carcinoma who received either 5-ALA (n = 187) or a placebo (n = 183) intravesically before cystoscopy. Each group underwent cystoscopy under visible white light and under fluorescent light followed by transurethral tumor resection. The primary study objective was to evaluate the 12-month recurrence-free survival.

Results: Slightly more patients with tumors were detected by using 5-ALA than by using the placebo (88.5% vs 84.7%). The mean numbers of tumor specimens per patient were 1.8 (5-ALA) and 1.6 (placebo). Intrapatient comparison of fluorescent light versus white light cystoscopy in patients randomized to receive 5-ALA showed a higher tumor detection rate with fluorescent light than with white light cystoscopy. In patients receiving 5-ALA cystoscopy, the percentage of lesions that would not have been detected in these patients by white light cystoscopy ranged between 10.9% (pT1) and 55.9% (atypia). Progression-free survival was 89.4% (5-ALA) and 89.0% (placebo) (P = .9101), and recurrence-free survival 12 months after tumor resection was 64.0% (5-ALA) and 72.8% (placebo) (P = .2216).

Conclusions: In comparison to the placebo, 5-ALA cystoscopy did not increase the rates of recurrence-free or progression-free survival 12 months after tumor resection. Although more tumors per patient were detected in the 5-ALA group, the higher detection rate did not translate into differences in long-term outcome.

Editorial Comment

Fluorescence-guided diagnosis or resection of bladder cancer is a widely used tool and certainly even more widely disputed among urologists worldwide. Therefore, an independent assessment of its value is highly desirable.

This trial was the first double-blind, placebo-controlled, prospective randomized study and therefore the results are worth reading. In short, the mean number of tumor specimens per patient was higher with 5-ALA cystoscopy (1.8) than with placebo arm cystoscopy (1.6). The difference was not significant (P = .1178). Slightly more tumors were detected with 5-ALA cystoscopy than with placebo arm cystoscopy (88.5% vs 84.7%). In contrast to previous studies with 5-ALA the percentages of diagnoses with isolated CIS were rather low (5-ALA 1.6%; placebo arm 1.7%); those with concomitant CIS were 10.8% (5-ALA) and 12.0% (placebo arm). Interestingly, recurrence-free survival rates at 12 months were 64.0% (5-ALA cystoscopy) and 72.8% (placebo arm cystoscopy) (not significant).

In conclusion, this multicenter trial had different results than previous single center trials with dedicated interest in 5-ALA resection. Further multicentric, blinded trials are needed to establish the real value of this potentially helpful adjunct to urologic surgery.

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NEUROLOGY & FEMALE UROLOGY

Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse

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Background: The use of standardized mesh kits for repair of pelvic-organ prolapse has spread rapidly in recent years, but it is unclear whether this approach results in better outcomes than traditional colporrhaphy.
Methods: In this multicenter, parallel-group, randomized, controlled trial, we compared the use of a trocar-guided, transvaginal polypropylene-mesh repair kit with traditional colporrhaphy in women with prolapse of the anterior vaginal wall (cystocele). The primary outcome was a composite of the objective anatomical designation of stage 0 (no prolapse) or 1 (position of the anterior vaginal wall more than 1 cm above the hymen), according to the Pelvic Organ Prolapse Quantification system, and the subjective absence of symptoms of vaginal bulging 12 months after the surgery.
Results: Of 389 women who were randomly assigned to a study treatment, 200 underwent prolapse repair with the transvaginal mesh kit and 189 underwent traditional colporrhaphy. At 1 year, the primary outcome was significantly more common in the women treated with transvaginal mesh repair (60.8%) than in those who underwent colporrhaphy (34.5%) (absolute difference, 26.3 percentage points; 95% confidence interval, 15.6 to 37.0). The surgery lasted longer and the rates of intraoperative hemorrhage were higher in the mesh-repair group than in the colporrhaphy group ($P < 0.001$ for both comparisons). Rates of bladder perforation were 3.5% in the mesh-repair group and 0.5% in the colporrhaphy group ($P = 0.07$), and the respective rates of new stress urinary incontinence after surgery were 12.3% and 6.3% ($P = 0.05$). Surgical reintervention to correct mesh exposure during follow-up occurred in 3.2% of 186 patients in the mesh-repair group.
Conclusions: As compared with anterior colporrhaphy, use of a standardized, trocar-guided mesh kit for cystocele repair resulted in higher short-term rates of successful treatment but also in higher rates of surgical complications and postoperative adverse events. (Funded by the Karolinska Institutet and Ethicon; ClinicalTrials.gov number, NCT00566917.).

Editorial Comment

This paper is the result of an outstanding effort by several centers to bring up a decent comparative analysis between classic anterior colporrhaphy and transvaginal mesh correction for pelvic organ prolapse. The study enrolled approximately 400 patients and gathered two very similar groups to undergo the two procedures. Equation of factors such as BMI, age and time since menopause adds credibility to this cohort. It is a known concern that mesh placement involves a more demanding surgical expertise and familiarity with pelvic anatomy and also is associated with a higher rate of sexual dysfunction (1) and major surgical

complications, as the technique frequently involves the blind passage of needles to anchor mesh arms into the pelvic ligaments. This study corroborates that intraoperative complications may a bit higher indeed in the mesh group (blood loss, operative time, bladder perforation) but with low clinical impact (except for blood loss in 5 five cases of the mesh group which surpassed 500 mL). Sexual impairment was statistically equivalent for both groups regarding pain and satisfaction ($p > 0.05$). Objective results for organ prolapse were better for the use of mesh repair which is in accordance with other reports with similar follow up (1 year). A higher incidence of new stress urinary incontinence was detected and may result from overcorrection of the apical axis by the mesh. This may vary according to mesh design and placement technique (2).

The need to judiciously select the patients who are good candidates to undergo a mesh repair is obvious as it is not free from undesired effects. However, urologists are encouraged to pursue surgical expertise involving these innovative options as there is a continuous tendency to improve mesh designs and biomaterials.

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Solifenacin may improve sleep quality in patients with overactive bladder and sleep disturbance

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Objective: To examine the effect of solifenacin for not only overactive bladder symptoms but also sleep disturbance. Nocturia and urgency are independent factors for sleep disturbance.
Methods: Fifteen male patients with overactive bladder symptoms and sleep disturbance were enrolled in this study. The overactive bladder symptoms score (OABSS) and Athens insomnia scale (AIS) were used as a subjective questionnaire for overactive bladder symptoms and insomnia. The Actiwatch-16 (Mini-Mitter-Respironics, Inc., Bend, OR) was used as an objective measurement tool for insomnia. Total sleep time, sleep efficiency, sleep latency, wake-after-sleep onset, and number of awakenings were measured by the Actiwatch. We evaluated the changes of each parameter before and 8 weeks after the administration of solifenacin. Statistical comparisons before and after the administration were made using the Wilcoxon signed-rank test. To examine the relation between OABSS and AIS, Spearman's testing was used for correlations between independent variables and $P < 0.05$ was considered statistically significant.
Results: Total OABSS and total AIS were significantly improved after administration of solifenacin. The cat-

egories of urgency and nocturia in OABSS and the categories of awakening during the night and sleep quality in AIS were also significantly improved. The Actiwatch study showed that total sleep time and sleep efficiency were significantly improved. The decrease of AIS was significantly correlated with the decrease of urgency ($\rho = 0.635$, $P = 0.0175$) but not with nocturia.
Conclusion: The treatment of urgency by solifenacin may improve not only overactive bladder symptoms but also sleep disturbance.

Editorial Comment

In this interesting report by Takao et al. they objectively assess the impact of solifenacin on sleep disturbance in male patients suffering from OAB symptoms. They used an electronic simple device (Actiwatch) for 1 week before and after treatment and validated questionnaires to assess the effects of a daily drug use of 5 mg for 8 weeks.

Results confirmed an improvement in urgency and nocturia. A significant decrease in awakenings during the night and an improvement in quality of sleep were also detected.

Although multifactorial sleep disturbance can be at least partially deteriorated by nocturnal frequency, and therefore improving bladder capacity, decreasing afferent sensibility and night time urine overproduction are targets to be aimed at. In order to obtain more consistent data, prospective randomized placebo controlled studies and head-to-head comparison with other antimuscarinic agents are warranted.

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GERIATRIC UROLOGY

Low risk prostate cancer in men ≥ 70 years old: To treat or not to treat

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Objectives: Prostate cancer (CaP) in the aging male will become an increasingly important and controversial health care issue. We evaluated the outcomes between a variety of treatments for low-risk CaP in patients 70 years of age and older.
Methods and Materials: A total of 3,650 men diagnosed with CaP between 1989 and 2009 were identified in the Center for Prostate Disease Research database to be 70 years of age or older at time of diagnosis. Of these patients, 770 men met the D'Amico criteria ([13]) for low-risk disease and were treated with radical prostatectomy, external beam radiation therapy, or watchful waiting. Cox proportional hazard models were used to compare clinicopathologic features across treatment groups. Kaplan-Meier analysis was used to compare biochemical recurrence-free, progression-free, and overall survival.
Results: Of the 770 patient cohort, 194 (25%) chose radical prostatectomy, 252 (33%) chose external beam radiation therapy, and 324 (42%) were initially managed by watchful waiting with 110 (34%) of this subset ultimately undergoing secondary treatment. The median follow-up was 6.4 years. There were no significant

differences in distributions of race/ethnicity, number of medical comorbidities, or clinical stage across the treatment groups. Patients managed on watchful waiting without secondary treatment had the poorest overall survival on Kaplan-Meier analysis (P = 0.0001). Additionally, multivariate analysis confirmed this result for watchful waiting without secondary treatment as being a statistically significant predictor of overall mortality (HR 1.938, P = 0.0084).

Editorial Comment

There are clearly multiple biases confounding the results presented in this series as recognized by authors. Considering the study limitations, disease specific survival would limit confusing related to age and co-morbidities and is not informed in the article. However, Kaplan-Meier biochemical recurrence-free survival curves across treatment groups failed to achieve statistical significance (P = 0.08), envisaging similar disease specific survival across analyzed groups.

Furthermore, given the relatively short follow up time of watchful waiting (WW) without secondary treatment group - median (range) 4.3 (0.8–16.6) years, an expressive cancer specific mortality is not expected for patients genuinely presenting D'Amico criteria for low-risk disease (stage T1-2a, Gleason score ≤ 6, and PSA < 10 ng/mL).

On multivariable cox proportional hazards model predicting overall mortality, age at diagnosis, number of comorbidities and WW with no secondary treatment were the only statistically significant variables. Adds to that the fact that the mean age at diagnosis was lower in the primary RP group (72.2 ± 1.9) compared with the EBRT (74.1 ± 3.1), WW (75.7 ± 3.8), and WW with secondary treatment (74.5 ± 3.6) groups (P < 0.0001).

Last but not least, while important information such as the detailed protocol for those under WW was not described (number of cores per biopsy, number of biopsies, etc), neither the number of patients who despite disease progression kept under WW, it is fundamental to highlight that most of the described patients in this study present performance for active surveillance rather than WW. In this regard, treatment indication, timing and intent have different endpoints being symptoms, late and palliative for WW and biopsy, early and curative for active surveillance, respectively.

Certainly, most of these patients will not likely progress to the point of metastases, or cancer-specific death before they die of another cause if under well conducted and more stringent active surveillance protocol compared to WW.

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Diminished efficacy of bacille calmette-guérin among elderly patients with nonmuscle invasive bladder cancer

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Objective: Bacille Calmette-Guérin (BCG) is recommended as adjunctive therapy among patients with high-risk nonmuscle-invasive bladder cancer (BC). Given that immune response is attenuated with age, we set out to determine the impact of age on response to BCG.
Materials and Methods: We searched our prospective bladder information system and limited our search to patients with incident BC completely resected at transurethral resection (TUR) who completed a full induction course of BCG. We then analyzed the impact of age on outcome. Age was analyzed both dichotomously (greater or less than 75 years) as well as by 10-year increments. The main outcomes were recurrence or progression-free survival. Log-rank and multivariable Cox proportional-hazard analyses, adjusting for clinical and pathologic features (age, multifocality, pathologic stage, grade and associated carcinoma in situ, maintenance, and restaging) were used.
Results: This cohort included 238 patients. Baseline parameters were similar aside from tumor number. Progression-free survival differed between age groups when examined either dichotomously or via 10-year increments. The 2-year progression-free survival was 87% among patients < 75 years vs 65% in patients > 75 years (log rank $P < 0.001$). An age-dependent trend was noted when analyzed by 10-year increment (log-rank for trend $P = 0.011$). On multivariable analysis, age was an independent risk factor for progression (HR = 2.9, 95% CI 1.7-4.9). Recurrence-free survival was similar among age strata.
Conclusion: We demonstrated that advanced age is associated with higher progression rates despite BCG. The care of BC in the elderly population is of increasing concern and should be addressed in a prospective clinical study.

Editorial Comment

The only independent risk factor for progression in this cohort was age (≥ 75 years vs < 75 years) with a HR of 2.1 (95% CI 1.7-4.9), and maintenance therapy resulted in a statistically significant decrease risk of progression with a HR of 0.8 (95% CI .92-.64). Maintenance therapy significantly reduced the risk of recurrence in patients younger than 75 (HR 0.76; 95% CI .93-.60) as well as those older than 75 (HR 0.86; 95% CI .99-.60).

Progression was associated with age, even after controlling for BCG maintenance and re-resection in a very homogenous cohort where all patients had newly diagnosed bladder tumors (primary presentation), and that completed a full induction course of intravesical BCG, the only clinically used adjuvant therapy known to decrease progression. However data should be viewed with caution given the retrospective design, the unavoidable selection bias and the relatively small cohort.

It was previously suggested that elderly are more commonly exposed to statins and fibrin clot inhibitors (aspirin or coumadin); these exposures are known to alter BCG response. On the other hand, a worse pathophysiology could not be excluded in elderly and was previously proposed by others, although these studies are also deemed to selection bias (1).

Future studies are necessary to confirm these findings and to optimize cancer treatment of elderly.

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PEDIATRIC UROLOGY

Improved survival with lymph node sampling in Wilms tumor

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Objective: We sought to determine the impact of number of lymph nodes examined on survival for Wilms tumor (WT).
Methods: Data from the Surveillance, Epidemiology, and End Results and Florida Cancer Data System were queried for patients < 20 years of age with WT.
Results: Of 1805 WT patients, 1340 had lymph node (LN) data available following surgery. The mean age for the cohort was 3.3 ± 2.8 y. Most patients were White (78%), and non-Hispanic (78%). A total of 297 patients (22%) had 0 LN sampled, while 697 (52%) had 1-5 LN, 210 (16%) had 6-10 LN, and 136 (10%) had > 10 LN. Overall 5-y survival was 91%. By univariate analysis, 5-y survival was significantly lower for patients with 0 LN sampled (87% versus 91% 1-5 LN; 93% 6-10 LN; 95% > 10 LN, P = 0.005). Multivariate analysis confirmed a survival advantage for patients having 1-5 LN (HR 0.600, P = 0.016), 6-10 LN (HR 0.521, P = 0.048), and > 10 LN (HR 0.403, P = 0.039) compared with patients with 0 LN examined.
Conclusion: Failure to biopsy lymph nodes for WT patients not only increases the risk of local recurrence due to understaging and inadequate adjuvant therapy, but is also an independent prognostic indicator of lower survival.

Editorial Comment

The authors' use data from two large population based cancer registries in order to determine the impact of lymph node sampling on overall survival for pediatric Wilms tumor patients. Adequate data was found on 1340 patients. Patients were divided into groups on the basis of their lymph node sampling. 22% of patients had no lymph nodes sampled; 52% had 1-5 lymph nodes; 16% had 6-10 lymph nodes; and 10% had greater than 10 lymph nodes sampled. On multivariate analysis they found statistically significant survival advantage for those patients who had lymph nodes sampled versus those who did not. This advantage increased among groups with greater numbers of lymph nodes sampled.

While review of cancer registries to obtain this kind of information in a retrospective fashion always has inherent flaws, the large number of patients and multivariate analysis would certainly suggest benefit

from lymph node sampling. As the authors concede, it is difficult to know whether the survival advantage is secondary to under-staging, resulting in inadequate adjuvant therapy, or if there is improved regional disease control or both. In either case, pediatric urologists and surgeons who care for these children, as well as the pathologists that they work, with should be cognizant of such data when operating on these patients and reviewing their specimens.

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Are stone protocol computed tomography scans mandatory for children with suspected urinary calculi?
Johnson EK, Faerber GJ, Roberts WW, Wolf JS Jr, Park JM, Bloom DA, Wan J
Department of Urology, University of Michigan Medical Center, Ann Arbor, Michigan 48109-5330, USA
Urology. 2011; 78: 662-6

Objective: To examine the clinical utility of noncontrast-enhanced computed tomography (NCCT) in pediatric patients with urolithiasis who progressed to surgery. Although NCCT is routine for the evaluation of adult patients with suspected urolithiasis, its routine use in the pediatric population is tempered by concern about radiation exposure.
Methods: We conducted a retrospective chart review of all pediatric patients who had undergone surgery for urinary stones from 2003 to 2008 at our institution. The imaging modalities used, surgery type, stone composition, 24 - hour urinalyses, and relevant predisposing conditions were characterized.
Results: A total of 42 pediatric patients (24 males and 18 females) were treated during the 6-year period. The average age was 11.3 ± 5.3 years (range 2.7 - 25.4), and the most common treatment modalities were shock wave lithotripsy (28%) and ureteroscopy (22%). A discernible risk factor or cause of urolithiasis was absent in 21 patients (47%). A review of imaging studies found 38 with stones visible on ultrasonography and/or abdominal plain film. A total of 21 patients underwent NCCT, in addition to ultrasonography and/or abdominal plain film. Of these, only 5 patients required NCCT for the diagnosis or management of their stone.
Conclusion: Nearly 90% of pediatric patients treated for symptomatic urolithiasis could have completed their evaluation and treatment without undergoing NCCT. For children who present with signs and symptoms suggesting urinary calculi, an initial evaluation and imaging with ultrasonography and abdominal plain film might suffice, avoiding the radiation of NCCT.

Editorial Comment

While non-contrast CT scans have become the gold standard for imaging of urinary tract stones in the adult population, legitimate concerns have been raised regarding the widespread use of CT scans in the pediatric population. These authors performed a retrospective review of their pediatric stone patients over a five year period of time to determine the usefulness of CT scans compared with ultrasound and/or KUB. They were able to identify 42 patients during the study period and found that 90% of the stones were visible on ultrasound and/or KUB.

This study brings to light, the importance of using clinical judgement when evaluating children with suspected stone disease. By starting with an ultrasound and KUB first, the vast majority of children can be spared significant radiation exposure. One can always fall back to CT scan in those cases where the initial imaging studies are indeterminate.

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INFORMATION FOR AUTHORS

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Editor, International Braz J Urol

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• Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:
• Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:
• Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

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UROLOGICAL CALENDAR

ERUS'11: European Robotic Urology Symposium
Hamburg, Germany
October 5 - 7, 2011
E-mail: nfo@erusmasterclass.com
Website: www.erus2011.com

1st Joint Meeting of the EAU Section of European Society of Female and Functional Urology (ESFFU) and the EAU Section of Genito-Urinary Surgeons (ESGURS)
Tübingen, Germany
October 6 - 8, 2011
E-mail: m.koops@congressconsultants.com
Website: www.esffu-esgurs.uroweb.org

67th Annual Meeting of the American Society for Reproductive Medicine (ASRM)
Orlando, FL, USA
October 15 - 19, 2011
E-mail : asrm@asrm.org
Website : www.asrm.org

31st Congress of the Société Internationale d'Urologie
Berlin, Germany
October 16 - 20, 2011
E-mail : congress@siu-urology.org
Website : www.siucongress.org

84th Congress of the SIU
Rome, Italy
October 23 - 26, 2011
E-mail : info@siu.it
Website : www.siu.it

Argentina Congress of Urology 2011
Buenos Aires, Argentina
02 Nov 2011 - 04 Nov 2011
E-mail: sau@sau-net.org
Website: www.sau-net.org

3rd Multidisciplinary Meeting on Urological Cancers
Barcelona, Spain
November 4 - 6, 2011
E-mail: emuc-meeting2011@congressconsultants.com
Website: www.emucbarcelona2011.org

Renal Week 2011 American Society of Nephrology
Philadelphia, PA, USA
November 8- 13, 2011
E-mail: email@asn-online.org
Website: www.asn-online.org

4th ESU MC Female and functional reconstructive Urology
Berlin, Germany
November 11 - 13, 2011
E- mail: esu@uroweb.org
Website: www.uroweb.org

29th World Congress on Endourology and SWL
Kyoto, Japan
November 30 - 03 December, 2011
E-mail: wce2011@congre.co.jp
Website: www.congre.co.jp/wce2011

XXXIII BRAZILIAN CONGRESS OF UROLOGY
November 22 - 26, 2011 - Florianópolis, SC, Brazil

UM PASSADO INESQUECÍVEL, UM FUTURO GLORIOSO

O nascimento é um momento de intensa emoção. Com uma nova vida, sentimentos se renovam e a esperança de um futuro melhor fica mais forte. A criação da Sociedade Brasileira de Urologia, em 1926, trouxe para os profissionais da área a confiança de que a prática profissional seria mais difundida e aprimorada em todo o país. Hoje, 85 anos após a sua fundação, o urologista brasileiro tem a certeza de que a sociedade cumpriu muito bem o seu papel e de que o seu futuro será ainda mais glorioso do que a sua história.

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