



# International

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*View of the laparoscopy unit. (Page 108)*

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# International Braz J Urol

Official Journal of the Brazilian Society of Urology - SBU

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# International Braz J Urol

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## ***EDITOR'S COMMENT***

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### **Time to Acknowledge and Plan for the Future**

Dear Readers and Contributors,

Our International Braz J Urol began the year 2011 with changes in the Editorial Board. We would like to reserve this space for a message from Prof. Francisco J. B. Sampaio, who during the past 10 years as Editor-in-Chief of the Journal has without question significantly raised its national and international scientific standard. Prof. Fernando Kim, has now assumed the recently created position of International Editor and Prof. Miriam Dambros, is the current Editor-in-Chief.

## Past Editor's Comment

Dear Readers, Authors and Colleagues of the International Braz J Urol,

It is probably not in the best of interests of the Journal to remain as Editor for more than 10 years. Also, the position is tiring and consumes a considerable portion of the Editor's academic time. I was appointed to the position in 2000 and therefore I consider that it is time to step down as Editor-in-Chief.

During this period, the International Braz J Urol (IBJU) experienced many changes and developments. The IBJU is now recognized as a major publication in urology and is well known all over the world. The IBJU is now a truly international journal and our on-line version receives more than 45,000 visits every month from more than 60 different countries. Also, during the last five years, the Journal published contributions from more than 30 countries.

At this moment, according to SCImago Journal and Country Rank ([www.scimagojr.com](http://www.scimagojr.com)), the IBJU is "Number One" in the ranking of Urological, Surgical and Surgical Specialties Journal in Latin America and the Iberian Peninsula. The IBJU has also gained a major place in the world urological literature. The Journal has been covered by Thomson Reuters (ISI) Current Contents / Clinical Medicine since January 2008 and has been included in the Science Citation Index Expanded, accessible through the Web of Science. Our current unofficial Impact Factor is 1.2, calculated in the same way that ISI generates its Impact Factors. Our official Impact Factor will appear in the 2010 Journal Citation Report (JCR), which will be released in mid-2011, with respect to articles published in 2008 and 2009. We are confident that the official Impact Factor will be even higher than 1.2. This is thanks to the enthusiastic efforts and dedication of our Readers, Authors, Editorial Board and Ad-hoc Reviewers who have devoted their time to our Journal.

In early December 2010, I asked for my replacement and Dr. Miriam Dambros was appointed to my position. Dr. Dambros is Professor of Urology at Federal University of São Paulo and has all attributes necessary for the position. I have been working on the transition with Dr. Dambros during several weeks and I have now passed on the editorship of the Journal to my successor.

I am profoundly grateful to you all for your invaluable support and friendship during these past years, which has been of utmost importance for the great success of our Journal.

  
**Francisco J. B. Sampaio, M.D.**  
Editor-in-Chief, IBJU, 2000-2010

## **International Editor's Comment**

Dear Colleagues,

It is an honor to write you as the International Editor of the International Braz J Urol.

Together with Prof. Miriam Dambros, the new Editor-in-chief of the IBJU, we can reassure our readers as to the continuation of the Journal's mission to inform, educate and establish a productive rapport with the urological community.

Since the IBJU was founded in 1975 by Dr. Alberto Gentile, the editors, reviewers and authors have promoted and developed a pivotal instrument of urological knowledge, in their native language, allowing the Brazilian urological community to exchange their knowledge and experience via articles, comments and case reports.

Undoubtedly, due to the dynamic editorship of Prof. Francisco Sampaio, the IBJU evolved in the last decade to International status with the recruitment of worldwide expert's contributions. Not only the prestige of the journal has risen to a new level, but also the volume and quality of manuscript submissions has achieved new high standards.

Therefore, the Brazilian Society of Urology (SBU) and IBJU governing board have created the position of International Editor of the Journal

As the International Editor of the IBJU it is my privilege to serve as the liaison between the IBJU and the international urologic community to continue the promotion of the journal narrowing our relationships, improving communication and encourage scientific submissions from international authors and institutions.

***Fernando J. Kim, M.D., FACS***

International Associate Editor

## Editor's Comment

Firstly may I say that I feel extremely honored to have been appointed to the post of Editor-in-Chief of the IBJU. I am very flattered to assume the coordination and grateful for the possibility of the challenge to further improve our Journal.

At this particular time there are no words to thank;

- the commitment and work of Professor Francisco Sampaio who for these past 10 years with dedication and patience has made the IBJU a fundamental and reputable scientific journal. I thank him as Editor-in-Chief and as a member of the Brazilian Society of Urology in the name of all Brazilians urologists.

- the Associate Technical Editor, Dr. Luciano A. Favorito, Associate Editors, Dr. Gerard C. Freire, Miguel Srougi, Dr. Wachira Kochakarn, Dr. Mark S. Soloway, Dr. Claude Schulman, Video Section Editor, Dr. Philippe E. Spiess, Assistant Medical Editor, Richard Medeiros, Urological Survey Committee, Dr. Athanase Billis, Dr. Andreas Bohle, Dr. Sean P. Elliott, Dr. Fernando Kim, Dr. Adilson Prando, Dr. M. Chad Wallis, Dr. Manoj Monga, Dr. Steven P. Petrou and all Consulting Editor members.

The time involved and personal experience were essential to the growth of the IBJU. I look forward to closely working with you.

- the efficiency and good job that Ricardo de Moraes has done in running the Editorial Office.
- Prof. Modesto Jacobino for his genuine interest in the growth of IBJU.
- the readers, authors and Brazilian urological community because they believe and have become partners in the Journal. I am anxious to receive your comments and feedback on how you think the journal is progressing and what could be done to improve the IBJU.

In the position of Editor-in-Chief of the IBJU some changes were proposed such as the creation of the position of Editor for the Portuguese language, which will be occupied by Prof. Silvio Tucci, University of São Paulo - Ribeirão Preto, aimed at facilitating the dissemination of the journal in the Brazilian community. Along with the English edition will be sent via Compact Disc, the Portuguese version of the Journal's content. The newly created position of International Editor will be occupied by Prof. Dr. Fernando Kim, who is a faithful friend and collaborator and has the task of increasing internationalization of our journal.

Another point that I would like to comment on is that since 2009 we have attempted to install the Editorial Manager system as a work platform for the submission of papers. This is a mission that is at this moment one of my top priorities, which we can start using very soon. I would also like to offer my total commitment and firm interest in encouraging the submission and publication of articles from Brazilian authors. The main reason for the existence of IBJU is to provide a vehicle for the disclosure of basic science, clinical scientific articles and reviews of good quality within our specialty, by Brazilian researchers. To this end, the Brazilian Society of Urology will organize meetings with residents, preceptors and the Editor-in-Chief as well as a blog where interested individuals can resolve their doubts and suggest changes in the journal.

Finally, may I re-confirm my total commitment to the further growth of the IBJU with the sincere hope that our Journal will continue to be the source of pride for all Brazilian urologists.

***Miriam Dambros, M.D.***

Editor-in-Chief

# Novel Concepts in Male Infertility

**Sandro C. Esteves, Ashok Agarwal**

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## ABSTRACT

Extraordinary advances have been achieved in the field of male infertility in the last decades. There are new concepts in sperm physiology and several modern tools for the assessment of spermatogenesis kinetics in vivo. New tests using molecular biology and DNA damage assays allow the clinician to correctly diagnose men so far classified as having idiopathic male infertility. In the field of treatment, microsurgery has increased success rates either for reconstruction of the reproductive tract or the retrieval of spermatozoa for assisted conception. Emerging evidence suggests that life-style and environmental conditions are of utmost importance in male fertility and subfertility. This review discusses several concepts that have changed over the last years, such as the duration of the spermatogenic cycle in humans, Y-chromosome infertility, the reproductive potential of non-mosaic Klinefelter syndrome men, the impact of paternal age and sperm DNA in male infertility, the role of antioxidants in the treatment of infertile men, the predictive factors and techniques for sperm retrieval in non-obstructive azoospermia, and the microsurgical treatment of clinical varicoceles. Whenever possible, levels of evidence are provided as suggested by the Oxford Center of Evidence-based Medicine.

**Key words:** male infertility, semen, azoospermia, varicocele, assisted reproductive techniques, evidence-based medicine  
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## INTRODUCTION

Approximately 8% of men in reproductive age seek medical assistance for fertility-related problems. Of these, 1-10% carries conditions that compromise the reproductive potential; varicocele accounts for 35% of the cases (1). The urologist's role in this field cannot be underestimated. He/she is trained to diagnose, counsel, provide medical or surgical treatment whenever possible and correctly refer the male patient for assisted conception. By integrating the reproductive team, the urologist is responsible for the above-cited tasks and to perform surgical sperm retrieval.

The urologist should also be aware of the recently published evidence that have challenged several established concepts in male infertility. This

review discusses the main concepts that have changed over the previous years and provides the levels of evidence, whenever possible, as suggested by the Oxford Center of Evidence-based Medicine (2).

## DURATION OF THE SPERMATOGENIC CYCLE

Misell et al. (2006) have shown for the first time that the time from initiation of spermatogenesis to appearance in the ejaculate is approximately 64 days, significantly shorter than the previously suspected 70 to 80-day period (3). Men with normal sperm concentrations ingested  $^2\text{H}_2\text{O}$  daily and semen samples were collected every 2 weeks for up to 90 days.  $^2\text{H}_2\text{O}$  label incorporation into sperm DNA was

quantified by gas chromatography/mass spectrometry, allowing calculation of the percent of new cells. The overall mean time to detection of labeled sperm in the ejaculate was  $64 \pm 8$  days (range 42-76). They also observed biological variability, thus contradicting the current belief that spermatogenesis duration is fixed among individuals. All subjects achieved greater than 70% new sperm in the ejaculate by day 90, but plateau labeling was not attained in most, suggesting rapid washout of old sperm in the epididymal reservoir (4). Their data also suggested that in normal men, sperm released from the seminiferous epithelium enter in the epididymis in a coordinated manner with little mixing of old and new sperm before subsequent ejaculation. This is also a new concept, because it had been suggested that because of mixing, in any segment of the epididymal duct, the population of sperm would be heterogeneous in age and biological status.

## Y-CHROMOSOME INFERTILITY

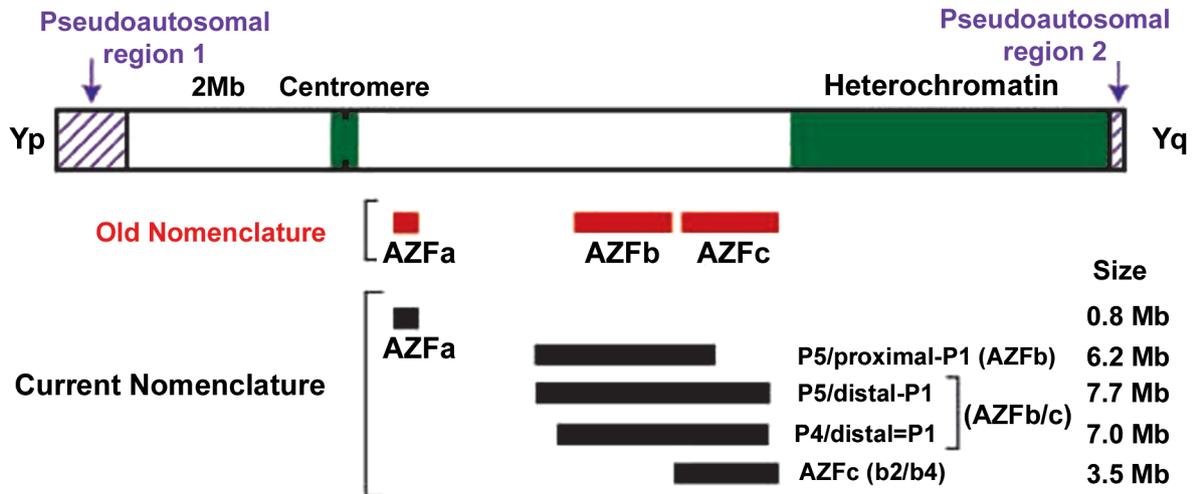
Y-chromosome infertility is characterized by azoospermia or severe to moderate oligozoospermia, although rare cases of mild oligozoospermia ( $5\text{-}20 \times 10^6$  sperm/mL semen) may occur. Men with Y-chromosome infertility have no obvious symptoms, but physical examination may reveal small testes and/or cryptorchidism or varicoceles. One report suggested that a specific deletion in the AZFc region (gr/gr) might increase the susceptibility to testicular cancer (5). The prevalence of Y-chromosome microdeletions is estimated to be about 1:2000 to 1:3000 males; the frequency in males with azoospermia or severe oligozoospermia is about 5%-12%, although a marked difference is reported in different world regions (6).

Clinically available molecular testing may reveal microdeletions in the long arm of the Y-chromosome. The diagnosis of Y-chromosome microdeletions consists of a series of polymerase chain reaction amplifications within relatively broad regions of the Y-chromosome. Originally, three regions were defined: AZFa, AZFb and AZFc (azoospermia factor), which map on the long arm (Yq) from the centromere to the telomere (7). A fourth region, named AZFd, located between AZFb and AZFc was also reported.

The relative frequency of individual microdeletions are 60%, 5% and 16% for AZFc, AZFa and AZFb regions, but combined deletions occur in about 15% of cases (8). Because deletions tend to occur between large palindromic repeats, Repping et al. (2002) proposed a more appropriate nomenclature using the name of the flanking repeats for the types of recurrent deletions (7) (Figure-1).

Pregnancies can be achieved by in vitro fertilization (IVF) using intracytoplasmic sperm injection (ICSI) in males with Y-chromosome infertility exhibiting oligozoospermia or azoospermia with retrievable testicular sperm (9,10). The presence of a deletion has no apparent negative effect on fertilization or pregnancy and it does not increase the risk for birth defects in children conceived via assisted reproduction technology (ART) (11) (Level C evidence). The presence of sperm in men with Y-chromosome microdeletions varies with the type of deletion. Testicular phenotypes associated with microdeletions in the AZFa region are the most severe and include Sertoli cell-only (SCO) pattern on testis histology (10). Testicular phenotypes associated with microdeletions restricted to AZFc ranged from azoospermia to moderate oligozoospermia whereas AZFb microdeletions are often associated to azoospermia. Individuals with AZFd microdeletions manifest the broadest range of testicular phenotypes. In partial and complete AZFc deletion azoospermic patients, sperm can be found in the testis in 70% of the cases. In contrast, the chance of finding sperm in azoospermic men with complete AZFa or AZFb deletions is unlikely (11) (Level C evidence). Large deletions involving multiple AZF regions generally present with testicular phenotypes similar to those restricted to AZFa (6).

Y-chromosome infertility is inherited in a Y-linked manner. Deletions are usually *de novo* and therefore not present in the father of the proband. Rarely, within a family, the same deletion of the Y chromosome can cause infertility in some males but not in others; hence, some fertile males with deletion of the AZF regions have fathered sons who are infertile (12). In pregnancies achieved from males with infertility caused by deletion of the AZF regions using ICSI, male offspring have the same deletion as their father.



**Figure 1** – Illustration of the Y chromosome in humans and the regions involved in fertility and infertility. Interstitial or terminal deletions that include AZFa, often mediated by recombination between the HERV15yq1-HERV15yq2 repeats, usually produce the severe phenotype of Sertoli-cell-only syndrome. Interstitial or terminal deletions that include AZFb and/or AZFb+c (hereafter designated AZFb/c) are mediated by recombination between palindromic repeats, either P5/proxP1, P5/distP1, or P4/distP1. These deletions usually result in azoospermia. Interstitial or terminal deletions that include AZFc only are mediated by recombination between the b2/b4 palindromic repeats and result in a variable phenotype, ranging from azoospermia and SCOS to severe or mild oligozoospermia. This type of deletion can occasionally be associated with normal fertility in younger males, with the phenotype worsening with age. Such individuals should consider cryopreservation of ejaculated sperm in early adulthood. Two partial deletions of AZFc, called b1/b3 and gr/gr, are considered polymorphisms. (Adapted from *Am J Hum Genet.* 71(4), Repping S et al., *Recombination between Palindromes P5 and P1 on the Human Y Chromosome Causes Massive Deletions and Spermatogenic Failure*, pages: 906-22, Copyright 2002, with permission from Elsevier).

## REPRODUCTIVE POTENTIAL OF NON-MOSAIC KLINEFELTER SYNDROME MEN

The frequency of Klinefelter syndrome (KS), a specific chromosomal abnormality (47,XXY), is 0.2% of male newborns and 11% of azoospermic men (13). The sterility of KS is due to the high prevalence of azoospermia present in 92% of KS men; the remainder have a median of 0.1 million sperm/mL. Nevertheless, sperm are found in 50% of cases on testicular exploration and pregnancy rates by ICSI range from 30% to 50% (13). None of the clinical parameters are predictive of success in sperm retrieval.

KS men fathered more than 60 children worldwide; ~50 had karyotype analysis all being normal (13,14). Sciurano et al. (2009) have shown that seminiferous tubuli with germ cells represents

only a minor fraction of all tubuli in men with non-mosaic KS. Using fluorescence in situ hybridization (FISH), they showed that meiotic spermatocytes are euploid, and thus can form normal, haploid gametes. Sertoli cells showed two marks for the X chromosome, meaning that they were 47, XXY (15). These new findings may explain the high rate of normal children born after testicular sperm extraction plus ICSI when applied to KS.

Sperm retrieval rate appeared to be lower (20%) in KS men who previously received exogenous androgens (13). Such treatment may suppress the hypothalamic-pituitary-testis axis, impairing FSH secretion and decreasing intratesticular androgen levels that could impair spermatogenesis. Ramasamy et al. (2009) showed that other medications leading to endogenous testosterone increase seem to benefit KS men. In their study, KS men with either normal or low baseline testosterone but who respond to medical therapy (aromatase inhibitors, clomiphene or human

chorionic gonadotropin) had a better chance of sperm retrieval (77% vs. 55%) (16) (Level C evidence).

## PATERNAL AGE AND INFERTILITY

There is a general belief that the fertility potential of older man is fairly well preserved. However, recent evidence support the concept that advanced paternal age is associated with an increase in sperm chromosomal aneuploidy (17,18). The risk for a father over 40 years-old to have a child with an autosomal dominant mutation equals the risk of Down syndrome for a child whose mother is 35-40 years-old. Also, fathers over the age of 40 had a 20% greater chance of having a baby born with a serious birth defect (18). Moskovtsky et al. (2006) demonstrated that the rate of sperm with fragmented DNA doubled in men 45 years and older compared to those less than 30 years old (19) (Level B evidence). Siddighi et al. (2007) showed increased necrosis, DNA damage and apoptosis while rapid progression and total motility declined with advancing male age beginning as early as age 35 (20). Plastira et al. (2007) demonstrated that increased age in infertile patients was associated with an increase in sperm DNA fragmentation and poor chromatin packaging, as well as with a decline in semen volume, sperm morphology and motility (21) (Level C evidence). The current findings may help to define better cut-off age limits for donor sperm banking guidelines.

## SPERM DNA INTEGRITY AND FERTILITY

In clinical practice, traditional semen analysis maintains its central role in the assessment of male fertility potential. However, in several cases abnormalities in the male genome characterized by damaged sperm DNA may be indicative of subfertility regardless of routine semen parameters (22).

Assays to evaluate sperm chromatin/DNA integrity can be divided in three groups (23): a) sperm chromatin structural probes using nuclear dyes (e.g. microscopic acridine orange test [AOT], sperm chromatin structural assay [SCSA], aniline blue test

[AB], chromomycin- A3 [CMA3] and toluidine blue [TB], b) tests for direct assessment of sperm DNA fragmentation (e.g. terminal deoxynucleotidyl transferase mediated dUTP nick end labeling assay [TUNEL] and single-cell gel electrophoresis assay [COMET], and c) sperm nuclear matrix assays (e.g. sperm chromatin dispersion test). Sperm DNA damage levels are significantly different between fertile and infertile men. The probability of fertilization in vivo and by intrauterine insemination (IUI) seems to be close to zero if the proportion of sperm cells with DNA damage exceeds 30% (DFI) as detected by SCSA (24) (Level B evidence). Semen samples containing >12% sperm with fragmented DNA (TUNEL) resulted in no pregnancies in IUI (25). Sperm DNA damage is negatively correlated with embryo quality and blastocyst formation in IVF cycles and with fertilization rates in both IVF and ICSI (26). However, successful pregnancies in IVF/ICSI can be obtained using semen samples with high proportion of DNA damage. Bungum et al. (2004) demonstrated that higher clinical pregnancy rates (52.9 % vs. 22.2 %) and delivery rates (47.1 % vs. 22.2 %) were obtained after ICSI as compared to IVF when semen samples with high levels of sperm DNA damage were used, as previously suggested (27) (Level B evidence). Despite these data, a recent meta-analysis failed to support the concept that DNA integrity testing was more predictive for IVF than ICSI, and even that such testing is predictive of pregnancy outcome either in IVF or ICSI (28) (Level A evidence).

The proportion of sperm with DNA damage was shown to be higher in men from couples with recurrent pregnancy loss compared to the general population or fertile donors (29). It is suggested that 39% of miscarriages could be predicted using a combination of sperm DNA integrity assays (30) (Level C evidence). Aitken and Krausz (2001) proposed that sperm DNA damage is promutagenic; mutations can occur after fertilization as the oocyte attempts to repair DNA damage prior to the initiation of the first cleavage. Mutations occurring at this point will be fixed in the germline and may be responsible for the induction of infertility, childhood cancer in the offspring and higher risk of imprinting diseases (31). So far, follow-up of children born after ICSI compared with children born after conventional IVF have not

been conclusive regarding the risks of congenital malformations, imprinting diseases and health problems in general (32).

Existing data justify the introduction of sperm DNA damage assessment into the male infertility workup, but current evidence are not strong enough to provide a clinical indication for routine use in infertility evaluation (23,28) (Level A-B evidence). Sperm DNA damage testing may be indicated in un-

explained or idiopathic infertility, when a traditional semen analysis is normal and no evident female reproductive system pathologies can be revealed, and in selected cases of recurrent miscarriage. The ART method of choice can be recommended based on sperm DNA damage results and testicular instead of ejaculated sperm may be used for ICSI attempting to optimize reproductive outcomes in selected cases. Whether sperm DNA damage can be treated, allow-

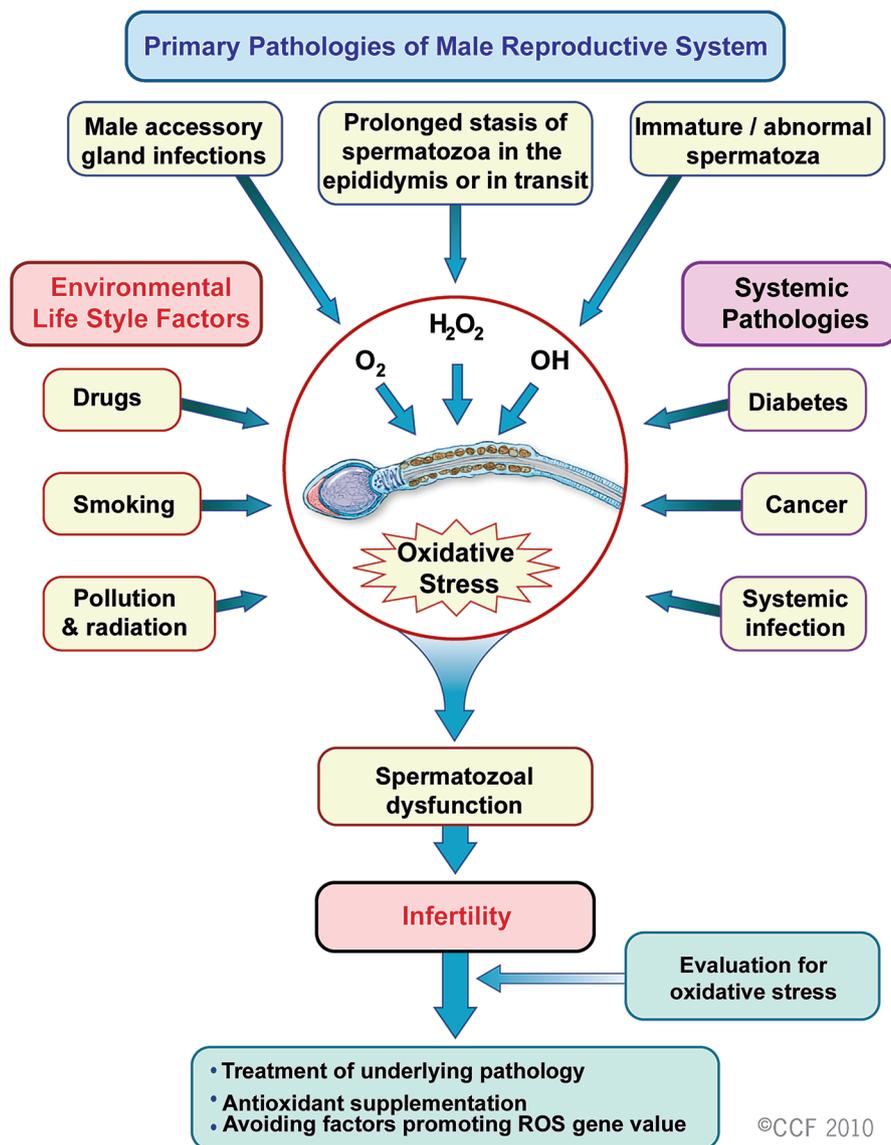


Figure 2 – Relationship of the primary pathologies of the male reproductive system, oxidative stress and infertility.

ing these couples to switch from ICSI to IVF/IUI or even achieve a pregnancy in a natural way, remains to be elucidated (33).

## OXIDATIVE STRESS AND INFERTILITY

Oxidative stress (OS) is induced by reactive oxygen species (ROS) (33). Normal levels of ROS are required for sperm physiology, but excessive levels of ROS can negatively affect sperm quality (Figure 2). The OS-induced sperm damage has been suggested to be a significant contributing factor in 30–80% of all cases of male infertility (34). The generation of ROS can be exacerbated by environmental, infectious, and lifestyle etiologies (35-37). For example, exposure to cigarette smoke generates high levels of OS, directly increasing seminal leukocyte concentrations and seminal ROS generation, and decreasing seminal levels of the antioxidant enzyme superoxide dismutase (SOD). Smoking decreases concentrations of the seminal plasma antioxidants thereby reducing the oxidant scavenging capacity of the spermatozoa and seminal fluid (38).

Oxidative stress can be measured using direct and indirect assays. Direct assays measure the net oxidative sum of the balance between ROS production and intra- and extracellular antioxidants that scavenge ROS. The most used direct assay measures malondialdehyde, one of the final products of sperm cell membrane lipid peroxidation. Quantification of sperm DNA damage has also been used as a direct assay of intracellular ROS-induced oxidant injury (39). The most common indirect method for seminal ROS measurement is via chemiluminescence. Luminol or lucigen probes can be used for quantification of redox activities of spermatozoa; they have well established reported ranges for fertile and infertile populations thus bringing clinical relevance to its use (39).

Recent reports have focused on the therapeutic management of OS in male infertility. Varicocele increase OS levels in the testes as well as semen, and varicocelectomy may decrease seminal OS, increase seminal concentrations of antioxidants and also improve sperm quality (40) (Level C evidence). In recent years, interest has increased in the role of antioxidants and B vitamins as modulators of fertility

outcome. The antioxidants alpha-tocopherol (Vitamin A), ascorbic acid (Vitamin C) and the retinoids (Vitamin A) are potent scavengers of ROS. Deficient vitamin-B concentrations cause elevated homocysteine concentrations and impair the remethylation cycle of phospholipids, proteins, DNA, and RNA. These processes are essential in spermatogenesis. Wong et al. (2002) demonstrated that folic acid (5 mg) and zinc phosphate (66 mg) caused a 74% increase of total normal sperm count in subfertile men (41) (Level B evidence). Boxmeer et al. (2009) reported for the first time that a low folate concentration in seminal plasma is associated with more sperm DNA damage in fertile men (42). Folate shortage increases DNA fragility due to the misincorporation of uracil instead of thymine. Greco et al. (2005) studied a large cohort of infertile men with >15% DNA-fragmented spermatozoa treated with either 1 gram of Vitamin C and E daily or placebo for two months, and demonstrated that the percentage of DNA-fragmented spermatozoa was reduced, but with no effects on the sperm parameters (43). The authors further went on to demonstrate that supplementation with vitamins E and C significantly increased rates of clinical pregnancy and implantation following ICSI (44) (Level B evidence). Recently, a case series study suggested that an increased intake of antioxidant-rich food or antioxidant supplements (see appendix) by men with high levels of sperm DNA fragmentation or lipid per-

### Appendix

Antioxidant-rich food:  $\beta$ -carotene (carrots, spinach, tomatoes, papaya, guava, cherries, melons, peaches), vitamin C (guava, kiwi, mango, pineapple, melons, strawberries, berries, tomatoes, broccoli, cabbage, oranges, lemons and other citrus fruits), vitamin E (lettuce, peanuts, almonds, coconut, corn, soy or olive oil; wheat and corn germ; cereals), zinc (asparagus, potatoes, vegetables, eggs, fish). Commercial multivitamins most often contain  $\beta$ -carotene (5000 IU), vitamin C (60 mg), vitamin E (30 IU), and zinc (15 mg).

oxidation may result in an improvement in gestational outcomes for couples with recurrent embryo losses (45) (Level C evidence).

### **PREDICTIVE FACTORS AND TECHNIQUES FOR SPERM RETRIEVAL IN NON-OBSTRUCTIVE AZOOSPERMIA**

To date, there are still no absolute preoperative predictive factors for successful sperm retrieval (SR), although the probability seems to depend on the biopsy technique. Microdissection testicular sperm extraction (micro-TESE) has been shown to be more successful in sperm retrieval than a single biopsy or multiple random biopsies (46,47) (Level C evidence). Moreover, micro-TESE seems to have less effect on testicular function because it spares vessels during dissection and removes less tissue than random biopsies (48).

The concept that elevated FSH levels are associated with male sterility has now been challenged. Serum FSH is an indirect reflection of the global spermatogenic function and testis histology. In cases of diffuse maturation arrest (MA), adequate control feedback from germ cells and Sertoli cells exists despite the absence of sperm production (49). Sperm retrieval techniques can obtain sperm from the testicle even in cases of elevated FSH, but their results depend on the retrieval method. Bromage et al. (2007) reported that the probability for sperm retrieval in non obstructive azoospermia (NOA) men with elevated FSH are lower using random biopsy TESE (50), while Ramasamy et al. (2009) demonstrated nearly identical retrieval rates by micro-TESE of ~60% regardless of FSH levels (51) (Level B evidence).

Testicular histology is considered the best predictor for successful sperm retrieval in NOA. However, even the combination of histology and FSH results provides only a 'fair' accuracy rate of 0.74 (52) (Evidence level B). Nonetheless, Esteves et al. (2006) have shown that SR by micro-TESE were significantly higher in cases of hypospermatogenesis or MA (100% and 75%, respectively) as compared to SCO (32%) (53), thus highlighting the concept that even the more adverse histological pattern cannot determine if sperm are present elsewhere in the testis.

Recently, the importance of surgical treatment prior to sperm retrieval in NOA men has been highlighted. Inci et al. (2009) reported that treatment of clinical varicoceles prior to SR increased the chance of obtaining testicular sperm using micro-TESE in a group of NOA individuals with clinical varicoceles (54). Retrieval 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) (Level C evidence).

### **MICROSURGICAL TREATMENT OF CLINICAL VARICOCELES**

Although several studies demonstrated the beneficial effect of the surgical treatment of clinical varicoceles in infertility (40,55), a recent meta-analysis concluded that treatment of varicocele in men from couples with otherwise unexplained subfertility could not be recommended (56) (Level B evidence). This meta-analysis was challenged by Ficcaro et al. (2006), who argued that less than half of the studies in the Cochrane review included patients with abnormal semen analysis and palpable varicocele and demonstrated that its methodology and statistical power was poor, thereby minimizing its significance against varicocele repair (57). The most recent meta-analysis on varicocelectomy unequivocally demonstrated that the chances of obtaining a spontaneous conception were 2.8 times higher in the varicocelectomy group as compared to the group of patients who received either no treatment or medication (58) (Level A evidence). Recently, it has been shown that treatment of clinical varicoceles may also improve the outcomes of assisted reproduction in couples with varicocele-related infertility. Esteves et al. (2010) observed higher pregnancy rates after ICSI in the group of men who underwent microsurgical varicocele repair before ART (60.3% versus 45.0%), and logistic regression showed that the chance of obtaining a clinical pregnancy was increased by 69% if the varicocele had been treated before ICSI (OR: 1.69, 95% CI 1.00–2.84). Also, the chance of having a miscarriage after ICSI was significantly reduced by 2.3 times if the varicocele had been treated (OR: 0.433; 95% CI 0.22-0.83; P=0.01) (59). (Level C evidence).

To date varicoceles are treated using different techniques. A recent systematic review including 4,473 individuals concluded that open microsurgical inguinal or sub-inguinal varicocelectomy techniques resulted in higher spontaneous pregnancy rates with fewer recurrences and postoperative complications than laparoscopic, radiologic embolization and macroscopic inguinal or retroperitoneal varicocelectomy (60) (Level A evidence).

## CONCLUSIONS

The entire duration of the spermatogenic cycle is shorter (~60 days) than the previously suspected 70 to 80-day period. About 10% of the infertile male population previously misdiagnosed as idiopathic have de novo Yq microdeletions, and the presence or absence of sperm (ejaculated or retrieved) vary depending on the specific deletion. Although no treatment exists, ICSI may be effective but the male offspring will inherit the same deletion as their father. In ~50% of non-mosaic KS azoospermic men testicular sperm are found by micro-TESE. Children born after ICSI using testicular sperm from KS men have normal karyotype because the minor foci of germ cells into the seminiferous tubuli are euploid. Sperm quality declines with paternal age beginning as early as age 35, and it may explain certain cases of male infertility, recurrent miscarriages and the occurrence of autosomal dominant, single gene disorders in offspring. Abnormalities in the male genome characterized by damaged sperm DNA may be indicative of male subfertility regardless of normal routine semen parameters. DNA integrity testing is now clinically available and results may predict reproductive outcomes. Oxidative stress is associated with sperm quality and infertility. Therapeutic measures to decrease OS, including lifestyle modifications, varicocelectomy in selected cases and the use of vitamins/antioxidants, show promising results. In the subset of men with NOA, FSH levels are not predictive of SR or sterility. Micro-TESE yields the best SR rates in NOA; success may be optimized by surgical treatment of clinical varicoceles or by medical therapy in non-mosaic KS men. Microsurgical varicocelectomy is associated with lower recurrence

and complications. Spontaneous and assisted-conception conception may be increased after repair of clinical varicocele. We hope that our review will provide a better understanding of evolving concepts in the field of male infertility to urologists and male infertility specialists. This increased knowledge will no doubt aid in the better management and treatment of the infertile male.

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## CONFLICT OF INTEREST

None declared.

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## Constipation and LUTS - How do They Affect Each Other?

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### ABSTRACT

*Context:* Urinary bladder and rectum share a common embryological origin. Their autonomic and somatic innervations have close similarities. Moreover, the close proximity of these two organ systems could suggest that dysfunction in one may influence, also mechanically, the function of the other. Therefore, it is not surprising that defecation problems and lower urinary tract symptoms (LUTS) occur together, as reported in the literature.

*Objective:* To study the relationship between constipation and LUTS focusing on what is evidence-based.

*Evidence acquisition:* We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) database in February 2010 to retrieve English language studies (from 1997 to 2009) and the 2005, 2006 and 2007 abstract volumes of the European Association of Urology (EAU), American Urological Association (AUA) and International Continence Society (ICS).

*Evidence synthesis:* We present the findings according to the studied population in four groups: (a) children, (b) middle-aged women, (c) elderly and (d) neuropathic patients. Most published studies that correlated rectal and bladder dysfunction were carried out in children or in young women. On the other hand, there are few studies regarding the association between constipation and LUTS in the elderly and in neuropathic patients.

*Conclusions:* Several studies in children documented that constipation is linked to urinary tract problems, including infections, enuresis, vesicoureteral reflux and upper renal tract dilatation. The underlying pathophysiology of these findings has not yet been clearly defined. Studies in middle-aged women also support a high prevalence of constipation among patients suffering from urinary tract dysfunction. Furthermore, an association between constipation and urinary incontinence, as well as between constipation and pelvic organ prolapse, has been suggested. The only prospective study in constipated elderly with concomitant LUTS demonstrates that the medical relief of constipation also significantly improves LUTS. Finally, the available data on neuropathic patients suggest that stool impaction in the rectum may mechanically impede bladder emptying. However, most of the studies only include a small number of patients, are not prospective and are uncontrolled. Therefore, there is a need for large-scale, controlled studies to further improve evidence and to provide a valid recommendation for all groups, especially for the elderly and neuropathic patients.

**Key words:** *constipation; defecation; urinary tract; urinary tract diseases; urinary incontinence*

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### INTRODUCTION

The urinary bladder and the rectum have a common embryological origin in the cloaca. The motor nerve supply of each is provided by the para-

sympathetic outflow arising from S2-S4. The same is true for the external (striated) anal and for the external (striated) urethral sphincter; both are innervated by the pudendal nerve, arising from the Onuf's nucleus in S2-S4. In healthy individuals bladder and rectum

function are “in harmony” (1). However, constipation and lower urinary tract symptoms (LUTS) can occur concomitantly in children, women, the elderly, as well as in neuropathic patients.

Autonomic reflex interaction between the urinary bladder and the distal part of the gastrointestinal tract has been investigated in animal models and humans (2). It has been demonstrated that anal stimulation abolishes a prevailing detrusor contraction. On the other hand, distension of the urinary bladder in man produces an increase in internal anal sphincter pressure. This response is abolished by blockade of the thoracolumbar sympathetic outflow by epidural anaesthesia, indicating a spinal reflex arc (2).

The coincidence of defecation problems and LUTS reported in the literature may have several different aetiologies: (a) it may be that rectum and bladder are affected by the same neuropathology; (b) that dysfunction in one system may impede the neighbouring organs and structures mechanically, e.g. stool impaction from severe constipation may impede voiding; or (c) severe straining due to constipation may induce changes in the pelvic floor musculature, resulting in pelvic organ prolapse (POP) and urinary incontinence.

Most studies that correlated rectal and bladder dysfunction were carried out in children or in middle-aged women, but there is only one prospective cohort study, to our knowledge, regarding constipation and LUTS in the elderly (1). One of the difficulties to conduct clinical studies, including bowel dysfunction is the subjective aspect associated with the definition of constipation (3). Some studies used self-applied questionnaires where the patients could define themselves as constipated or not. Only recently, has chronic functional constipation been clearly defined (4).

The aim of this review was to study the relationship between constipation and LUTS, focusing on what is evidence-based and what can be recommended so far from the diagnostic and therapeutic point of view.

## **EVIDENCE ACQUISITION - SEARCH STRATEGY**

A literature search was performed in the Medical Literature Analysis and Retrieval System

Online (MEDLINE) database in February 2010 to retrieve English language studies (from 1997 to 2009) on the association between constipation and LUTS.

For retrieving the references in MEDLINE we used the following medical subject heading terms: “constipation” (major subject descriptor) and “defecation”, “urinary tract”, “urinary tract diseases”, “urinary tract infections”, “urinary incontinence” or “urinary retention” (subject descriptors). Furthermore, we searched the abstract volumes of the annual meetings of 2007, 2008 and 2009 of the European Association of Urology the American Urological Association and the International Continence Society meetings.

## **DEFINITION OF CONSTIPATION**

Constipation is an end-point defined by a constellation of symptoms, including infrequent passage of stool, faeces that are either large, hard or in small pieces, abdominal pain, palpable stool in the abdomen, stool in the rectal vault or faecal soiling. Functional constipation (FC) is considered a symptom-based disorder that is characterized by both decreased frequency and hard consistency of stools, as well as symptoms relating to difficult evacuation (5). Table-1 presents the Rome III criteria for chronic functional constipation in adults and in children (4). Other terms and definitions have been used by some authors. Obstructive defecation was defined as difficulty in passing stool, hard stool, straining for more than 15 min., or incomplete evacuation, occurring at least weekly (6). Anal incontinence was defined as involuntary leakage of solid or liquid faeces or gas (7). Finally, dysfunctional elimination syndrome (DES) has been defined as any pattern of voiding or stooling that varies from the developmental norm (8).

## **EVIDENCE SYNTHESIS ACCORDING TO THE STUDIED POPULATION**

The studies on Constipation and LUTS will be presented and discussed, as well as the levels of evidence (LoE) and grades of recommendation (GR). The publications were organized according to the studied population in four groups: Children,

**Table 1** – Rome III criteria for defining chronic functional constipation in adults and children (4).**Adults**

Diagnostic criteria\*

1. Must include two or more of the following:
  - a. Straining during at least 25% of defecations
  - b. Lumpy or hard stools in at least 25% of defecations
  - c. Sensation of incomplete evacuation for at least 25% of defecations
  - d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
  - e. Manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
  - f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

\* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

**Children**

Diagnostic criteria must include one month of at least two of the following in infants up to 4 years of age

1. Two or fewer defecations per week
2. At least one episode/week of incontinence after the acquisition of toileting skills
3. History of excessive stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large diameter stools which may obstruct the toilet

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.

Middle-Aged Women, Elderly, Neuropathic Patients. We were able to retrieve altogether 8 case-reports, 5 review studies, 3 case-control studies, 3 case-series, 6 cross-sectional studies, 5 cohort studies and 1 non-controlled clinical study. Table-2 lists the review articles on constipation and LUTS published so far. Table-3 and Table-4 lists the published studies on children and middle-aged women, respectively, and Table-5 shows the studies, only case-reports, in neuropathic patients.

## CONSTIPATION AND LUTS IN CHILDREN

Constipation is responsible for 3% of visits to a paediatrician and 25% of consultations with a gastroenterologist. Children diagnosed with constipation frequently have a poor appetite and have

been shown to have a lower calorie and fibre intake, lower body mass index and more frequent anorexia than non-constipated children (9). Some children voluntarily suppress the urge to defecate and they refuse toileting, although a strong need to defecate is present. Withholding behaviour over time can cause DES (8). This behaviour may be due to an impairment of learning subsequent to distress, trauma, disruption of routine, inattention or cognition difficulties and is often associated with the memory or expectation of pain at defecation. Also the presence of an anal fissure or an anal streptococcal infection may induce this behaviour (9). Environmental factors regarding toilets, lack of privacy, risk of bullying, limited access, lack of essential products for good hygiene and dirty bathrooms can all contribute in encouraging a child to withhold urine and stool while at school.

There are 12 studies addressing the relationship between constipation and LUTS on children

**Table 2** – Review studies on constipation and LUTS in the literature.

Refs.	Title
Halachmi et al. (2008)	The impact of constipation on the urinary tract system
Clayden et al. (2007)	Constipation and incontinence in childhood: two sides of the same coin?
Kistner M. (2009)	Dysfunctional elimination behaviours and associated complications in school-age children
Giramonti et al. (2008)	Variations in practice patterns regarding constipation in children with urinary tract infections
Merenda et al. (2004)	Bladder and bowel management for the child with spinal cord dysfunction

(10-21). Table-3 summarizes these studies, as well as, the LoE and GR, number of patients included in each study and their mean age. The important findings will be discussed in detail.

Loening-Baucke (10) published a cohort study evaluating the frequency of urinary incontinence and urinary tract infection in constipated children and the effect of successful treatment of constipation on urologic symptoms: 234 chronic constipated and encopretic children were evaluated before and at least 12 months after the treatment for constipation (mean follow-up = 15 months), which was successful in 52% of the children. In this group, relief of constipation resulted in disappearance of daytime urinary incontinence in 89% and night-time urinary incontinence in 63% of patients, and disappearance of recurrent urinary tract infections in all patients who had no anatomic abnormality of the urinary tract. This study showed that with treatment of the constipation, most children became clean and dry and recurrence of urinary tract infections was prevented (LoE 1B / GR B).

McGrath et al. (11) performed a prospective cross-sectional study of children with enuresis at presentation to a continence service. Data relating to the child's bowel habits, pattern of enuresis and other history items were obtained from parental questionnaires and paediatrician's assessments. Of the 277 participants aged 4.8-17.5 years (median 8.6 years), 100 (36.1%) were identified as constipated by the clinician, compared with only 39 (14.1%) from parental

reporting (Kappa = 0.155; P = 0.003). Constipation was high among children with enuresis, but was often not recognized by parents (LoE 2 / GR B).

Kajiwara et al. (15) retrospectively studied the differences between monosymptomatic and non-monosymptomatic enuresis on the basis of LUTS and constipation. Eighty-eight patients ( $9.8 \pm 3.1$  years old) were enrolled, 67 with monosymptomatic and 21 with non-monosymptomatic enuresis. Besides a history of urinary tract infections, mechanical obstructions and vesicoureteral reflux, constipation was also strongly associated with non-monosymptomatic enuresis compared to monosymptomatic enuresis (LoE 2 / GR C).

Bael et al. (12) studied the efficacy of treating urinary incontinence (UI) in children with concomitant functional fecal incontinence (FFI) or FC. After treatment of UI, FFI dropped from 32% to 21% (P = 0.035); for FC, the number of evaluated children was too small. Although the studied population was rather small, the outcome supports a mutual relationship between LUTS and bowel dysfunction (LoE 2 / GR B).

Koff et al. (13) performed a prospective cohort study to evaluate the prevalence of DES in children with vesicoureteral reflux and to determine whether functional bladder and/or bowel disorders influence the natural history or treatment of children with primary vesicoureteral reflux. One hundred and forty-three children with primary vesicoureteral reflux, that stopped spontaneously or was surgically corrected, were included. Unsuccessful surgical outcomes involving persistent, recurrent and con-

Constipation and LUTS

**Table 3** – Literature data on constipation and LUTS in children.

Refs.	Level of Evidence (ICUD)	GR	No. of Patients	Mean Age	Context
Loening-Baucke V. (1997)	1	B	234	9	Prospective cohort of paediatric patients to evaluate the frequency of urinary incontinence and urinary tract infections before and after treatment of constipation. Mean follow-up = 15 months.
McGrath et al. (2008)	2	B	277	8.6	Prospective cross-sectional study to identify the prevalence of constipation in children with enuresis (100% response rate)
Bael et al. (2007)	2	B	202	6-12	Prospective multicentre study to evaluate the prevalence of symptoms of disordered defecation before and after treatment for UI in children (89% after 6 month-follow-up). However, very limited population (few patients with constipation; n=14). No sample size estimation reported.
Koff SA et al. (1998)	2	B	143	Not reported	Prospective cohort study evaluating the prevalence of dysfunctional elimination syndrome in children with vesicoureteral reflux. Follow-up not reported.
Loening-Baucke V. (2007)	2	C	482	4-17	Retrospective study to evaluate the prevalence rates for constipation and urinary incontinence in children
Kajiwara M et al. (2008)	2	C	88	9.8	Retrospective study evaluating the prevalence of overactive bladder and constipation in children with primary enuresis

Constipation and LUTS

*Table 3 – Literature data on constipation and LUTS in children. – continued*

Refs.	Level of Evidence (ICUD)	GR	No. of Patients	Mean Age	Context
De Paepe et al. (2000)	2	C	20	4.45	Pelvic-floor therapy and toilet training in young children with dysfunctional voiding. No control group. Very small population.
Robson et al. (2005)	3	C	170	>3.5 (minimal age at inclusion)	Case-control study of patients with primary and secondary enuresis
Kasirga E et al. (2006)	3	C	69	63.5 months (case) and 82 months (control)	Case-control study to evaluate LUTS in children with functional constipation
Erickson BA et al. (2003)	3	C	46	7.7	Retrospective study evaluating the use of polyethylene glycol 3350 for constipation in children with dysfunctional elimination
Lucanto et al. (2000)	3	C	11	8.1	Case-series of paediatric patients with chronic constipation and LUTS to evaluate urodynamic characteristics and bowel motility.
Chrzan R et al. (2008)	4	C	50	9.6	Retrospective study evaluating the use of colonic enemas for persistent constipation in children with dysfunctional voiding. Very limited population. Only descriptive results.
Chase et al. (2004)	4	D	-	-	Consensus on children with bowel dysfunction and LUTS. No Delphi consensus statement reported

*LUTS = Lower urinary tract syndrome; ICUD = International Consultation on Urological Disease; GR = grades of recommendation.*

tralateral reflux occurred only in children with DES. The authors concluded that dysfunctional elimination syndromes are common and are often unrecognized in children with primary reflux. These syndromes are associated with delayed reflux resolution and an increased rate of breakthrough urinary tract infection, which leads more frequently to reimplantation surgery (LoE 2 / GR B).

Loening-Baucke (14) evaluated the prevalence rates for constipation, as well as of faecal and urinary incontinence in children attending primary care clinics in the United States. 482 children (7-17 years of age) were included in the study. The prevalence rate for constipation was 22.6% and was similar in boys and girls. The prevalence rate for faecal incontinence (> or = 1/week) was 4.4%. Faecal incontinence was associated with constipation in 95% of the patients. The prevalence rate for urinary incontinence was 10.5%; 3.3% for daytime only, 1.8% for day- and night-time and 5.4% for night-time urinary incontinence. Faecal and urinary incontinence were significantly more commonly observed in children with constipation than in children without constipation. Children with constipation had higher prevalence rates not only for faecal but also for urinary incontinence than children without constipation (LoE 2 / GR C).

De Paepe et al. (16) analysed the results after treating young children with LUTS and constipation, using a noninvasive training programme. Therapy consisted of keeping a voiding and drinking chart, instructions on proper toilet posture, daily rules for application at home, and if possible relaxation bio-feedback of the pelvic-floor muscles. Twenty children were treated and 13 had a good result (became dry during the day and night, and encopresis resolved). This study shows that pelvic-floor muscle- and toilet training can improve both LUTS and constipation, but the studied population was very small and there was no control group (LoE 2 / GR C).

## CONSTIPATION AND LUTS IN MIDDLE-AGED WOMEN

Constipation may affect 12 to 32% of middle-aged women (6,7). Women with constipation are more likely than men to seek medical attention or

use medication for this condition. There are 5 studies examining the prevalence of constipation and its association with LUTS and/or POP in middle-age women (6,7,22-24). These studies are summarized in Table-4.

Varma et al. (6) analysed data from a randomly selected cohort of 2,109 women, 40-69 years old, to describe the prevalence of obstructive defecation and identify associated risk factors. Obstructive defecation that occurred at least weekly was reported by 12.3% of women. Significant independent risk factors included vaginal or laparoscopic hysterectomy [odds ratio (OR) = 2.01; 95% confidence interval (CI) = 1.15-3.54], using three or more medications [1.81 (1.36-2.42)], symptomatic pelvic organ prolapse [2.34 (1.47-3.71)], urinary incontinence surgery [2.52 (1.29-4.90)], and other pelvic surgery [1.35 (1.03-1.78)]. Women who had undergone laparoscopic/vaginal hysterectomies or surgery for pelvic organ prolapse or for urinary incontinence had a nearly two times higher risk for obstructive defecation (LoE 2 / GR B).

Ewings et al. (22) performed a cohort study assessing risk factors for developing urinary incontinence following childbirth. A total of 723 women were recruited from the study. At 6 months post-partum, 45% of women reported some incontinence problems. Chronic constipation was the second strongest predictor for post-partum incontinence (OR = 1.86; 95% CI = 1.03-3.34), along with a pre-existing incontinence problem [4.49 (3.09-6.53)] and episiotomy in at least one delivery [1.96 (1.25-3.07)] (LoE 2 / GR C).

Soligo et al. (7) analysed the prevalence and patterns of constipation in women with urinary symptoms and/or genital prolapse. Seven hundred and eighty-six consecutive urogynaecological patients participated in a questionnaire and structured clinical assessment. Thirty-two percent of women were constipated. A genital prolapse of grade 2 or more occurred in 44% of women. A posterior colpocele was more frequent in constipated women (35% vs. 19%;  $p < 0.0001$ ), resulting in a risk factor for constipation (OR = 2.31; 95% CI = 1.63-3.27). By contrast, higher degrees of anterior colpocele appeared to protect against constipation [0.80 (0.66-0.96)]. Constipation correlated exclusively with posterior aspects of the pelvic floor support (LoE 2 / GR C).

**Table 4** – Literature data on constipation and LUTS in middle-aged women.

Reference	Level of Evidence (ICUD)	GR	Number of Patients	Mean Age (years)	Context
Varma MG et al. (2008)	2	B	2109	56	Population-based study to describe the prevalence of obstructive defecation and identify associated risk factors in middle-aged women
Ewings et al. (2005)	2	C	723	Not reported (>16 years at inclusion)	Prospective cohort study assessing risk factors for IU following childbirth. Follow-up = 76.9% after 6 months.
Soligo M et al. (2006)	2	C	786	60	Retrospective study to evaluate the prevalence and patterns of constipation in women with LUTS or prolapse. No detailed report of the urodynamic characteristics of the patients.
Ng et al. (2002)	3	C	320	45.1	Cross-sectional study evaluating the prevalence of anorectal dysfunction among women with LUTS.
Spence-Jones et al. (1994)	3	C	73	52	Case-control study to evaluate bowel dysfunction among patients with uterovaginal prolapse or stress UI.

*LUTS = Lower urinary tract syndrome; UI = urinary incontinence; ICUD = International Consultation on Urological Disease; GR = grades of recommendation.*

Spence-Jones et al. (24) performed a case-control study to investigate the aetiological importance of constipation in patients with uterovaginal prolapse and urinary stress incontinence. Twenty-three women with uterovaginal prolapse (mean age 57 years), 23 women with urinary stress incontinence (mean age 52 years) and 27 control women (mean age 52 years) were included. All three groups were comparable in terms of parity, age and birth weight of children. However, constipation as a young adult prior to the development of urogynaecological symptoms was significantly more common in women with uterovaginal prolapse (61% vs. 4%;  $P < 0.001$ ) and women with urinary stress incontinence (30% vs. 4%;  $P < 0.05$ ), compared to controls. At the time of consultation, 95% of the women with uterovaginal

prolapse were constipated, compared with only 11% of control women. Constipation, in addition to obstetric history, appears to be an important factor in the pathogenesis of uterovaginal prolapse and stress urinary incontinence (LoE 3 / GR C).

Ng et al. (23) evaluated the prevalence of anorectal dysfunction among women with LUTS. All 320 women who attended the urogynaecological outpatient clinic for urodynamic evaluation were requested to complete a structured questionnaire. Forty-nine (15.9%) women reported having anal incontinence. Constipation was reported by 100 (31.5%) of the women. A multiple logistic regression analysis revealed that the main risk factor associated with anal incontinence and constipation was the presence of uterovaginal prolapse (OR = 5.02; 95% CI = 2.19-11.5

**Table 5** – Case reports on constipation and LUTS in the literature (neuropathic patients).

Refs.	N. of Patients	Mean Age (years)	Context
Pannek et al. (2009)	2	62.5	Acute deterioration of bladder dysfunction due to constipation
Karatzoglou et al. (2008)	1	25	Patient with peripheral nerve sheath tumour presenting with constipation and urinary retention
Gividen et al. (2002)	1	14	Improvement of neuropathic bladder and urinary incontinence after antegrade continence enema procedure
Milne HJ (2006)	1	16	Pelvic Ewing's sarcoma. Constipation and recurrent urinary tract infections at presentation

LUTS = Lower urinary tract syndrome; UI = urinary incontinence.

for anal incontinence; OR = 1.78; 95% CI = 1.03-3.09 for constipation) (LoE 3 / GR C).

## CONSTIPATION AND LUTS IN THE ELDERLY

There is only one prospective cohort study, to our knowledge, evaluating the effect of alleviating constipation on LUTS in the elderly (1). Charach et al. studied fifty-two patients, aged 65-89 (mean 72 ± 13) years, with chronic constipation and LUTS, recruited from gastroenterology and urology clinics.(1) All patients were generally mobile, sensitive and continent. Before treatment of constipation was initiated, patients completed a questionnaire regarding their constipation pattern, LUTS, sexual function and mood. The follow-up was 4 months. Successful treatment of constipation increased the number of weekly defecations from 1.5 ± 0.9 to 4.7 ± 1.2 (P < 0.001); patients spent less time on the toilet (25 ± 2.1 versus 63 ± 1.9 min; P < 0.0001); fewer patients reported urgency (16 vs. 34; P < 0.001), frequency (25 vs. 47; P < 0.001) and burning sensation during urination (6

vs. 17; P < 0.05). At the same time, there was also an improvement in the scoring of urgency, frequency and burning sensation (from a baseline of 52 to 126, 131 and 95, respectively; P < 0.001). Urinary stream disturbances improved in 32 of the 52 patients (P < 0.001). Residual urine volume decreased from 85 ± 39.5 to 30 ± 22.56 mL (P < 0.001). There was also a significant decrease in the number of patients with bacteriuria events (5 vs. 17; P < 0.001), and an improvement in sexual activity and mood (P < 0.05). Treatment of constipation significantly improved LUTS, as well as, patient's mood, sexual activity and quality of life (LoE 2, GR B).

## CONSTIPATION AND LUTS IN THE NEUROPATHIC PATIENTS

Neuropathic lower urinary tract dysfunction and neuropathic colorectal dysfunction, as in patients with spinal cord lesions, share several similarities. The affected nerves causing the dysfunction are similar and the pattern of bowel and bladder dysfunction may change over the years (25). However, there are only

case-reports and review studies (26-30) addressing constipation and LUTS in neuropathic patients. Table-5 provides the case-report studies published so far.

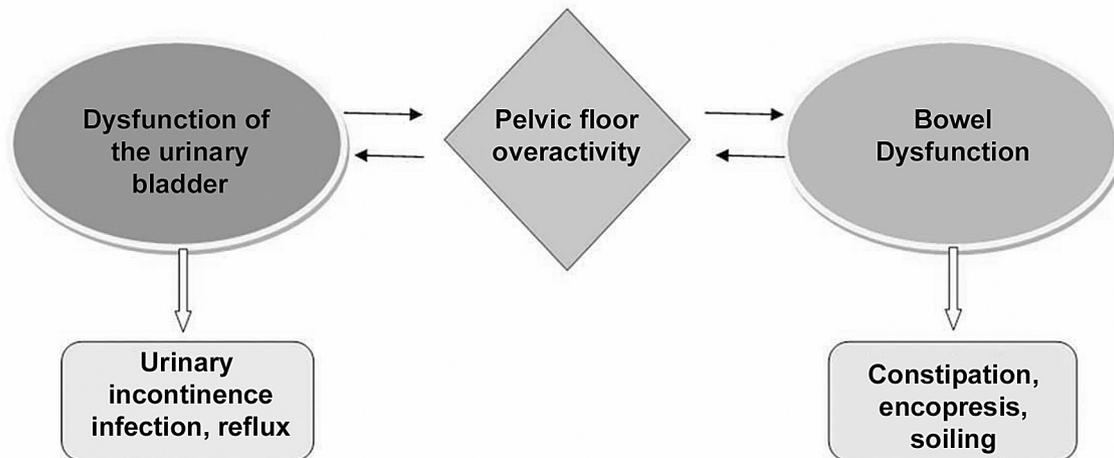
Only recently, Pannek et al. (26) published an interesting article reporting two cases with mechanical compression of the urinary bladder by an over distended bowel. The first patient (63 year-old male), who had post-traumatic paraplegia sub Th 7 since 17 years, was performing intermittent catheterization and was referred because of recurrent urinary tract infections and urinary incontinence. He showed a distended abdomen and palpable masses in the left lower quadrant. Digital rectal examination revealed massive stool masses. Computed tomography showed dilatation of the colon, completely filled with stool, compressing the bladder and the left ureter, resulting in upper urinary tract dilatation. The second patient (62 year-old male), with post-traumatic quadriplegia sub C 7 since 42 years, had undergone sacral deafferentation and implantation of a Brindley anterior root stimulator. He presented with urinary retention since 3 days, due to malfunction of the Brindley device. Physical examination revealed a minimally distended abdomen, but with palpable masses in the left lower quadrant. On digital rectal examination, lumps of hard stool were detected. Video-urodynamics demonstrated compression of the urinary bladder against the symphysis, making voiding impossible despite sufficient detrusor contractions. The patients were properly treated with evacuation by colonic hydrotherapy. After successful treatment of constipation, upper urinary tract dilatation resolved in the first patient, and in the second patient, after re-establishing the function of the Brindley device, with electrically driven defecation, stool impaction disappeared and electromicturition was possible. This case report shows that massive stool impaction due to neuropathic bowel dysfunction can mechanically impede bladder emptying.

## COMMENTS

Much attention has been focused on the evaluation of colon, rectum and anus in children with chronic constipation with or without encopresis, but little thought has been given to a possible association to urinary tract symptoms, such as day- and night-

time urinary incontinence, urinary tract infection, and urinary retention in these children (10), despite the well-known fact that the lower urinary tract and the lower bowel tract are interrelated structures (31). Anatomically bladder and rectum lay in close communication and share muscular structures of the pelvic floor. Nevertheless, it has been suggested that the distension of the rectum by stool impaction in constipated children presses on the bladder wall causing bladder outflow obstruction, as well as inducing detrusor overactivity (32). Urodynamic studies have reported detrusor overactivity in patients with functional constipation. Additionally, both, bladder overactivity and bowel dysfunction may lead to overactivity of the pelvic floor musculature, resulting in a high muscle tone, which again causes dysfunctional elimination of urine and faeces (Figure-1) (16). A comprehensive medical history along with physical examination must be done for every child either with LUTS and/or with chronic constipation and encopresis, bearing in mind the neighbouring organ systems. It has been shown that it is not enough only asking the parents about the bowel habits of the child, as constipation is frequently not recognized and reported by parents (11). Moreover, it is important to pay attention during the physical examination to findings suggesting stool impaction, such as abdominal masses and/or abdominal distension. Complementary ultrasound may provide additional information on filling condition of colon and rectum.

When a child presents with enuresis, it is for various reasons important to differentiate between monosymptomatic and non-monosymptomatic enuresis: it has been shown by Kajiwara et al. that constipation is more often found in association with non-monosymptomatic enuresis (15). Also in the setting of vesicoureteral reflux, it makes sense to search for constipation, because this condition can cause delayed reflux resolution and urinary tract infections. In this situation, successful treatment of constipation could avoid breakthrough urinary tract infections, which are often an indication for reimplantation surgery (13). In children with constipation and concomitant LUTS, adequate treatment of constipation also improves or abolishes LUTS. Loening-Baucke et al. performed a prospective study in this context: disappearance of day- and night-time urinary incontinence, only by



**Figure 1** – Overactivity of pelvic floor muscles following bladder and bowel dysfunction\*  
 \* Modified according to De Paepe et al. (16)

treating constipation, occurred in 89% and 63% of patients, respectively. Additionally, urinary tract infections disappeared in all patients who had no anatomic abnormality of the urinary tract (10).

Constipation in women may significantly impact overall quality of life (33). Bowel habits must be investigated, especially in women with previous hysterectomy, pelvic organ prolapse and urinary incontinence surgery, as it was shown that these conditions are independent risk factors for constipation, probably due to an iatrogenic lesion of the innervation (6,7,23). In contrast, constipation in young women is a risk factor for future uterovaginal prolapse and urinary stress incontinence (24). Constipation has frequently been described to increase the risk for pelvic organ prolapse (34). Pregnant women should have their bowel habits investigated, because there is good evidence that chronic constipation is a risk factor for postpartum urinary incontinence (22). When a pregnant woman presents with chronic constipation, one should treat this condition in time as an attempt to prevent postpartum urinary incontinence.

In community-based surveys, faecal incontinence (FI) is strongly associated with urinary incontinence and overactive bladder in both men and woman. Among nursing home patients, the association between urinary incontinence and FI is even stronger (35). It has also been shown that constipation and urinary symptoms are very common and disturbing in the

elderly population (1). In the only prospective study addressing this problem in the elderly, Charach et al. (1) have shown that the treatment of constipation, at the same time, also improves or abolishes the urologic symptoms as urgency, frequency and burning sensation can be significantly improved after treatment of constipation. Besides, improvements in sexual activity and mood have been reported. Thus, it is important to take into consideration that treatment of chronic constipation in elderly patients, by appropriate use of stool softeners, adequate fluid intake, exercise and disimpaction if necessary, may also improve or even cure the urological symptoms.

Indeed, there are only a few case-reports addressing the relationship between neuropathic bowel dysfunction and neuropathic urinary tract dysfunction (26-30). It has been documented that overdistended bowel can mechanically impede bladder emptying and can cause upper urinary tract dilatation (26). This has to be considered, especially at long term follow-up, when upper and/or lower urinary tract unexpectedly deteriorates; in this situation it is mandatory to exclude stool impaction by abdominal palpation and digital rectal examination, as well as by a plain abdominal X-ray, ultrasound and/or computed tomography. Colonic hydrotherapy is widely used for the treatment of this type of constipation. In these patients, with successful management of constipation, the urinary tract function can recover.

## CONCLUSIONS

Studies in children have linked constipation to urinary tract problems, including infections, enuresis, vesicoureteral reflux and upper renal tract dilatation. As a consequence of this interaction between bladder and bowel dysfunction, also overactivity of pelvic floor muscles is likely to occur. It is important in children with LUTS also to assess their bowel habits by taking a targeted history and proper clinical examination, as constipation may not be recognized and, thus, may not be reported by the parents. Studies in middle-aged women support a high prevalence of constipation among patients suffering from lower urinary tract dysfunction. There is some evidence for an association between constipation and urinary incontinence, as well as between constipation and POP and vice-versa. The only prospective study regarding the elderly population clearly shows that the medical relief of constipation significantly improves concomitant LUTS, which, in turn, improves the patient's mood, sexual activity and quality of life. Finally, the available data on neuropathic patients suggest that neuropathic bowel dysfunction with chronic constipation may mechanically cause urinary tract dysfunction. Chronic constipation and stool impaction may develop over many years, e.g. in spinal cord injured patients, and they are often subjectively unaware, of their condition which may be the reason for unexpected and otherwise unexplainable upper urinary tract deterioration and/or lower urinary tract dysfunction. In conclusion, despite the apparent relationship between constipation and LUTS, large scale, prospective, controlled studies are still needed, especially as regards the elderly and the neuropathic population.

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## CONFLICT OF INTEREST

None declared.

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## Rate of Renal Cell Carcinoma Subtypes in Different Races

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### ABSTRACT

*Purpose:* We sought to identify racial differences among histological subtypes of renal cell carcinoma (RCC) between black and non-black patients in an equal-access health care system.

*Materials and Methods:* We established a multi-institutional, prospective database of patients undergoing partial or radical nephrectomy between January 1, 2000 and Sept 31, 2009. For the purposes of this study, data captured included age at diagnosis, race, tumor size, presence of lymphovascular invasion, presence of capsular invasion, margin status, and tumor histology.

*Results:* 204 kidney tumors were identified (Table-1). Of these, 117 (57.4%) were in black patients and 87 (42.6%) were in non-black patients. Age at surgery ranged from 37 to 87 with a median of 62. Tumor size ranged from 1.0 to 22.0 cm with a median of 5.0 cm. Overall, tumors were composed of clear cell RCC in 97 cases (47.5%), papillary RCC in 65 cases (31.9%), chromophobe RCC in 13 cases (6.4%), collecting duct/medullary RCC in 2 cases (1.0%), RCC with multiple histological subtypes in 8 cases (3.9%), malignant tumors of other origin in 6 cases (2.9%), and benign histology in 13 cases (6.4%). Among black patients, papillary RCC was seen in 56 cases (47.9%), compared to 9 cases (10.3%) among non-black patients ( $p < 0.001$ ) (Table-2). Clear cell RCC was present in 38 (32.5%) of black patients and in 59 (67.8%) of non-blacks ( $p < 0.001$ ).

*Conclusions:* In our study, papillary RCC had a much higher occurrence among black patients compared to non-black patients. This is the first study to document such a great racial disparity among RCC subtypes.

*Key words:* kidney neoplasm; renal cell; carcinoma

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### INTRODUCTION

Renal cell carcinoma (RCC) is the seventh most common human malignancy, having accounted for approximately 59,702 new cancer cases in the United States in 2009 (1). The histological classification of RCC has undergone several major revisions, with the current 2004 World Health Organization (WHO) guidelines incorporating new cytogenetic findings and molecular markers that help guide diagnosis, prognosis, and therapy (2). RCC is now recognized to be a complex neoplasm consisting of several different tumor subtypes, each with distinct

genetic and clinical features. Previous population-based studies on racial differences in incidence patterns and outcomes of RCC have failed to account for the different histological subtypes of RCC (3). We sought to identify racial differences in the patterns of histological subtypes of RCC in a racially diverse, equal-access health care system.

### MATERIALS AND METHODS

We performed a multi-institutional, retrospective review of patients undergoing partial or radical nephrectomy between January 1<sup>st</sup>, 2000 and Sept 31<sup>st</sup>,

## RCC Subtypes in Different Races

2009. Our hospitals included a tertiary care academic center, a veteran's administration hospital, and an inner-city county hospital, ensuring a mixed ethnic population. All slides underwent centralized pathology review using the WHO 2004 Classification of renal cell histology to classify tumors into clear cell, papillary, chromophobe, or medullary/collecting duct varieties. We did not differentiate between papillary RCC type 1 and papillary RCC type 2. Data was collected by reviewing patient charts and capturing the following parameters: age at diagnosis, race, tumor size, presence of lymphovascular invasion, presence of capsular invasion, margin status, and tumor histology.

## RESULTS

Two hundred and four kidney tumors were identified (Table-1). Of these, 117 (57.4%) were in black patients and 87 (42.6%) were in non-black patients. Age at surgery ranged from 37 to 87 with a median age of 62. Among black patients the age range was 37 to 82 with a median of 63 and among non-black patients the age range was 40 to 87 with a median of 60.

Tumor size ranged from 1.0 to 22.0 cm with a median of 5.0 cm. The size of tumors among blacks ranged from 1.4 to 20.0 cm and from 1.0 to 22.0 cm in

**Table 1 – Baseline characteristics.**

	Black # (%)	Non-Black # (%)	Total	
Patient characteristics				
Number of patients	117 (57.4)	87 (42.6)	204 (100)	
Age				
Range	37 - 82	40 - 87	37 - 87	
Mean	60.3	64.1	61.9	
Median	63	60	62	
Under 65 years old	74/117 (63.2)	52/87 (59.8)	126/204 (61.8)	
65 years old or older	43/117 (36.8)	35/87 (40.2)	78/204 (38.2)	p = 0.61
Tumor characteristics				
Size (cm)				
Range	1.4 - 20.0	1.0 - 22.0	1.0 - 22.0	
Mean	5.9	5.1	5.6	
Median	5.0	4.9	5.0	
4 cm or less	41/113 (36.3)	35/82 (42.7)	76/195 (39.0)	
Greater than 4 cm and less than or equal to 7 cm	38/113 (33.6)	31/82 (37.8)	69/195 (35.4)	
Greater than 7 cm	34/113 (30.1)	16/82 (19.5)	50/195 (25.6)	p = 0.25
Lymphovascular invasion				
Yes	5/115 (4.3)	10/84 (11.9)	15/199 (7.5)	
No	110/115 (95.7)	74/84 (88.1)	184/199 (92.5)	p = 0.05
Capsular invasion				
Yes	10/115 (8.7)	11/84 (13.1)	21/199 (10.6)	
No	105/115 (91.3)	73/84 (86.9)	178/199 (89.4)	p = 0.32
Margin status				
Positive	6/115 (5.2)	5/84 (6.0)	11/199 (5.5)	
Negative	109/115 (94.8)	79/84 (94.0)	188/199 (94.5)	p = 0.82

non-blacks. There was no statistically significant difference in tumor size between blacks and non-blacks when subdivided into groups of 4 cm or less, greater than 4 cm and less than or equal to 7 cm, and greater than 7 cm (  $p = 0.25$ ).

The majority of tumors in blacks and non-blacks had absence of lymphovascular invasion (4.3% and 11.9%,  $p = 0.05$ ), absence of capsular invasion (91.3% and 86.9%,  $p = 0.32$ ), and negative surgical margins (94.8% and 94.0%,  $p = 0.82$ ).

Overall, tumors were composed of clear cell RCC in 97 cases (47.5%), papillary RCC in 65 cases (31.9%), chromophobe RCC in 13 cases (6.4%), collecting duct/medullary RCC in 2 cases (1.0%), RCC with multiple histological subtypes in 8 cases (3.9%), malignant tumors of other origin in 6 cases (2.9%), and benign histology in 13 cases (6.4%). Among black patients, papillary RCC was seen in 56 cases (47.9%), compared to 9 cases (10.3%) among non-black patients ( $p < 0.001$ ) (Table-2). Clear cell RCC was present in 38 (32.5%) of black patients and in 59 (67.8%) of non-blacks ( $p < 0.001$ ).

**COMMENTS**

Our study found a greater than four-fold increase in occurrence of papillary RCC in blacks when compared to non-blacks. This is the first study to document such a large ethnic disparity among RCC subtypes.

This phenomenon of neoplastic variability among different races has been observed in other urologic cancers. Prostate cancer is a well-studied malignancy that tends to behave differently among different races. Compared with whites, blacks are more likely to be diagnosed with prostate cancer at a younger age (4). Black patients with prostate cancer are also less likely to be treated with surgical intervention and have an overall lower survival (5).

There are many previously reported, large, population-based studies elucidating the racial disparities among patients with RCC. These reports, however, have focused on topics such as overall survival and access to health care. A recent paper by Stafford et al. found that blacks had an overall increase in incidence of renal cell carcinoma and decrease in survival rate when compared to other ethnicities (6). Zini et al. concluded that black patients with RCC were 50% less likely to undergo nephrectomy compared to white patients (7). A study by Brendt et al. also addresses the lower survival rate among blacks with renal cell carcinoma and proposes that this may be explained by both a higher number of comorbidities and lower rate of surgical treatment (8). While these studies have unearthed many interesting data trends among RCC cases, none have included information on histological subtypes of RCC.

Beyond the well-described association or renal medullary carcinoma with sickle-cell disease and trait in black patients, there has been very little reported regarding racial differences for the other RCC

*Table 2 – Race and tumor histology.*

<b>Tumor Histology</b>	<b>Black # (%)</b>	<b>Non-black # (%)</b>	<b>Total # (%)</b>	
RCC clear cell	38 (32.5)	59 (67.8)	97 (47.5)	$p < 0.001$
RCC papillary	56 (47.9)	9 (10.3)	65 (31.9)	$p < 0.001$
RCC chromophobe	6 (5.1)	7 (8.0)	13 (6.4)	$p = 0.40$
RCC collecting duct / medullary	2 (1.7)	0 (0.0)	2 (1.0)	$p = 0.22$
RCC multiple histologies	6 (5.1)	2 (2.3)	8 (3.9)	$p = 0.30$
Other malignancy	2 (1.7)	4 (4.6)	6 (2.9)	$p = 0.23$
Benign	7 (6.0)	6 (6.9)	13 (6.4)	$p = 0.79$
Total	117	87	204	

*RCC = renal cell carcinoma.*

histologies (9). Historically, clear cell tumors have accounted for 70-80% of RCC, followed by 10-15% for papillary, 3-5% for chromophobe, and 1-2% for medullary/collecting duct (10). Our reported 47.9% incidence of papillary tumors among black patients is the first of its kind and is more than four-fold the incidence of papillary tumors among non-black patients in our study. One explanation for this observation may be a genomic predisposition for blacks to express genes unique for the development of papillary RCC.

Papillary RCC is commonly found in two classic genetic syndromes, hereditary papillary RCC and hereditary leiomyomatosis and renal cell cancer syndrome. Papillary tumors have also previously been reported to be associated with acquired renal cystic disease. The chromosomal abnormalities for papillary tumors are distinct from the chromosome 3 and Von-Hippel Lindau gene abnormalities of clear cell tumors. Papillary tumors typically demonstrate trisomy of chromosomes 7 and 17 and loss of the Y chromosome. Mutations in the met-oncogene, which encodes hepatocyte growth factor, is the usual mutation for papillary tumors, which usually display multicentricity and hypovascularity. As expected with the new era of targeted therapies for RCC, unique molecular agents separate from tyrosine kinase inhibitors are being developed for papillary tumors. If black patients with RCC truly have a predisposition for expression of papillary type tumors, they may benefit from early counseling and treatment with novel agents targeting this unique tumor.

More recently, papillary RCC has been subdivided into type 1 and type 2, with type 2 tumors exhibiting more aggressive clinicopathological features and worse prognosis (11). Our retrospective analysis does not allow statements regarding the influence of tumor subtype on clinical course and prognosis following treatment. As such, we do not present any outcomes data and do not differentiate between subtypes of papillary RCC. Of note, there have been studies demonstrating no differences in disease-free survival between papillary and clear cell RCC (12).

One must also consider the possible influence of confounding factors on the variable expression of RCC subtypes. Previous studies have shown that there is a predisposition among males and patients with end stage renal disease to develop papillary RCC (13,14).

This potential bias should be taken into consideration when designing future studies aimed to capture racial differences observed among RCC subtypes.

## CONCLUSION

We report for the first time, to our knowledge, that black patients seem to have an increased risk of developing papillary RCC than the general population. This result needs to be confirmed by large, population-based studies that examine different RCC histologies against a wide range of demographic, geographic, and environmental factors. Given the complex genetic and molecular basis for RCC and its role in response to adjuvant treatments, race and ethnicity may be important factors when counseling patients regarding prognosis and treatment outcomes.

## CONFLICT OF INTEREST

None declared.

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**EDITORIAL COMMENT**

We have known for a while that renal cell carcinomas (RCC) are more common in blacks compared to non-Blacks and Asians. Not only more common, RCC tend to be more aggressive in blacks, with a higher disease-specific mortality even when tumor size and stage are independent variables. Black patients have a significantly higher incidence rate and lower survival rate than all other races/ethnicities even when having more localized cancer.

This study lists the rates of different types of renal cell carcinoma in a population composed of many ethnicities. In blacks, almost half of all tumors were papillary RCC, compared to only 10% in non-blacks. This disparity is not commonly addressed. In addition, it found a much lower rate of clear cell

RCC in blacks, which is not a common finding in the literature. The readers could have benefited by data on survival or progression, which unfortunately the study lacks. Nonetheless, given such racial disparities in renal cell carcinoma incidence in this one study, one should consider expanding and confirming these findings that may help elucidate biological, behavioral and environmental factors that can potentially be addressed.

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**EDITORIAL COMMENT**

Renal cell carcinoma (RCC) tends to manifest variable prognoses and outcomes. Previous articles have already pointed toward prognostic parameters including pathological subtypes and ethnic origin. Yet the issue of race was not fully addressed. Epidemiologic literature showed shorter survival in Black Americans with RCC. Tripathi et al. concluded that the overall survival for metastatic RCC was significantly shorter for Black Americans. Vaishampayan et al. had a similar conclusion for local RCC, emphasizing a higher incidence, poorer outcome in Black patients with a similar age and stage. However, the histology subtypes disparities were not mentioned, demonstrating the advantage of the recent manuscript based on data that was retrieved from an equal-access health care system. Stafford published a major study comparing ethnic groups (White, Black, Hispanic and Asian -Pacific) concluding that Black patients tend to have a higher incidence and a shorter survival while Asian patients demonstrate the opposite. Yet even this article did not point to the histology subdivision.

Herein we can appreciate an important study advancing our knowledge regarding the correlation between race and RCC histology subtypes. Further studies should investigate the papillary predominance

of the RCC in the black population while paradoxically demonstrating a poorer prognosis than what was known previously for that histological subtype.

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## Risk of Catecholamine Crisis in Patients Undergoing Resection of Unsuspected Pheochromocytoma

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### ABSTRACT

*Purpose:* To report the risk of catecholamine crisis in patients undergoing resection of unsuspected pheochromocytoma.

*Materials and Methods:* Over a four-year period, we retrospectively identified four patients who underwent resection of adrenal pheochromocytoma in whom the diagnosis was unsuspected based on preoperative clinical, biochemical, and imaging evaluation.

*Results:* None of the patients exhibited preoperative clinical features of catecholamine excess. Preoperative biochemical screening in two patients was normal. CT scan performed in all patients demonstrated a nonspecific enhancing adrenal mass. During surgical resection of the adrenal mass, hemodynamic instability was observed in two of four patients, and one of these two patients also suffered a myocardial infarct.

*Conclusion:* Both surgeons and radiologists should maintain a high index of suspicion for pheochromocytoma, as the tumor can be asymptomatic, biochemically negative, and have nonspecific imaging features. Resection of such unsuspected pheochromocytomas carries a substantial risk of intraoperative hemodynamic instability.

*Key words:* adrenal gland neoplasms; imaging; surgery; pheochromocytoma; catecholamines

*Int Braz J Urol. 2011; 37: 35-41*

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### INTRODUCTION

While there is widespread awareness of the classical clinical and radiological features of pheochromocytoma, it is perhaps less well known that 10% of pheochromocytomas are not associated with symptoms of excess catecholamine production, and up to 35% of pheochromocytomas have atypical imaging findings (1-5). Accordingly, the diagnosis may be unsuspected, and an indeterminate adrenal or retroperitoneal mass that is actually a pheochromocytoma could undergo resection without preoperative commencement of biochemical blockade. Such a patient is then at risk for a potentially a life-threatening intraoperative catecholamine crisis. However,

while the risks of iodinated contrast administration and percutaneous biopsy have been reported in these unsuspected pheochromocytomas (6-8), to our knowledge, the risk of surgery in this population has not been well described. We recently encountered several patients who underwent surgical resection of unsuspected pheochromocytomas. Therefore, we undertook this study to report the risk of catecholamine crisis in patients undergoing resection of unsuspected pheochromocytoma.

### MATERIALS AND METHODS

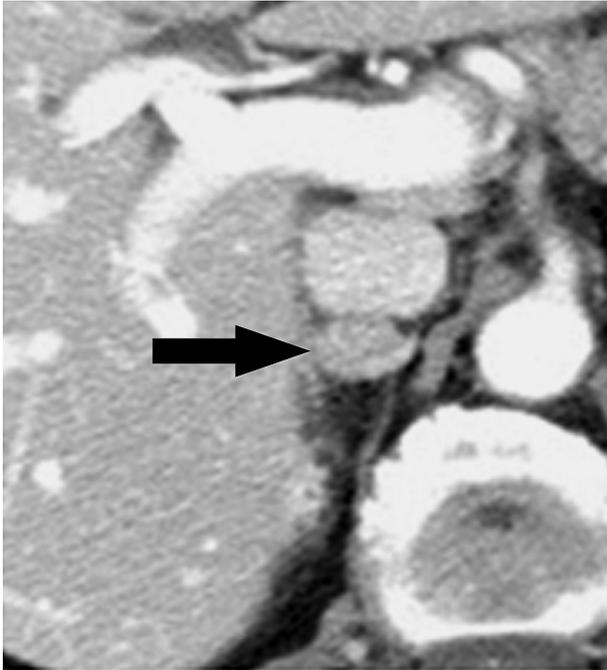
This was a retrospective study approved by our Committee on Human Research with waiver of

the requirement for informed consent. Four cases of pathologically proven pheochromocytoma that underwent attempted surgical resection were identified by the study authors between 2004 and 2007. All available imaging studies and medical records of these patients were reviewed by the principal investigator. Preoperative imaging consisted of CT scan examination obtained with multiple contiguous axial images performed in the venous phase following intravenous contrast agent in all four patients with

additional delayed phases obtained in two patients. One of the patients also underwent whole body PET scan after the administration of 16.4 milliCurie intravenous fluoro-2-deoxy-D-glucose (FDG) and utilizing attenuation-corrected regional emission images. None of the patients underwent imaging with iodine-131-meta-iodobenzylguanidine. The diagnosis of pheochromocytoma was confirmed by pathology of the surgically resected specimen in all four patients.

**Table 1** – Clinical, imaging, and operative characteristics of four patients undergoing resection of an unsuspected pheochromocytoma.

Age (yrs)	Sex	Indication for CT	Laboratory Studies	Imaging Modality/Findings	Intraoperative/ Postoperative Course	
1	76	F	Staging of cecal tubulovillous adenoma.	Normal 24 hour urinary vanillyl-mandelic acid and normetanephrine.	CT scan with intravenous contrast agent, venous and delayed phases. Homogeneously enhancing 1.3 x 1.7 cm right adrenal mass, <50% washout on delayed images (141 HU to 87 HU).	Open right hemicolectomy and adrenalectomy. Intraoperative blood pressure rise to 200/100 mm Hg followed by drop to 70/30 mm Hg on administration of antihypertensives. Transient ventricular ectopy with bigeminy. Postoperative troponin and EKG changes of non Q-wave myocardial infarction.
2	64	F	Abdominal pain.	None.	CT scan with intravenous contrast agent, venous phase. Heterogeneously enhancing 4.0 x 4.5 cm retroperitoneal mass arising from the left adrenal gland.	Open exploratory laparotomy and adrenalectomy. Intraoperative blood pressure rise to 220/110. Normotensive following expeditious removal of lesion.
3	49	M	Staging of metastatic melanoma.	None.	PET and intravenous contrast-enhanced portal venous phase CT. Heterogeneously enhancing 2.8 x 2.9 cm left adrenal mass, SUV of 4.8.	Laparoscopic adrenalectomy. Uneventful intraoperative and postoperative course.
4	25	F	Restaging of Hodgkin's lymphoma previously treated by chemotherapy and radiotherapy.	Normal plasma metanephrine and normetanephrine.	CT scan with noncontrast, intravenous contrast-enhanced portal venous, and delayed phases. Homogeneously enhancing 2.2 x 1.8 cm right adrenal mass, <50% washout on delayed images (130 HU to 107 HU).	Laparoscopic adrenalectomy. Uneventful intraoperative and postoperative course.

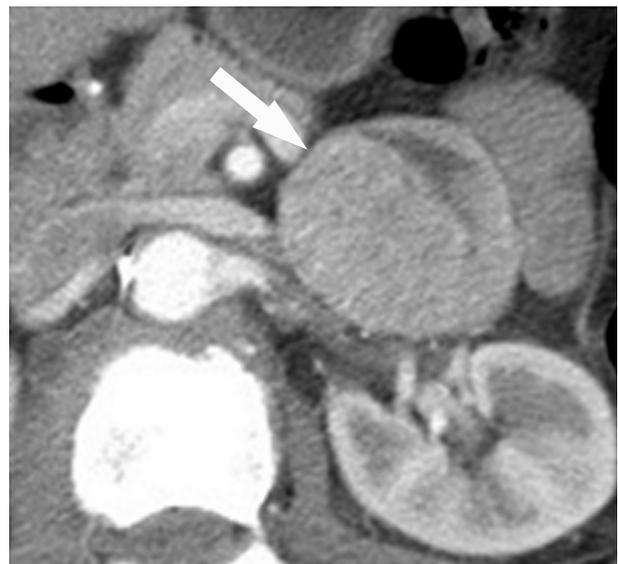


**Figure 1** – Axial contrast-enhanced portal venous phase CT scan in a 76 year old woman undergoing preoperative staging of a cecal mass (Case 1 in Table-1). A homogeneously enhancing right adrenal mass (arrow) is seen, and showed less than 50% washout on delayed images (not shown). The patient proceeded to right hemicolectomy and adrenalectomy, because the working diagnosis before surgery was of possible adrenal metastasis. Surgery was complicated by hemodynamic instability and a postoperative non-Q wave myocardial infarction. Final pathology revealed a cecal tubulovillous adenoma and an adrenal pheochromocytoma.

## RESULTS

The clinical and radiologic characteristics and intraoperative and postoperative course of the four patients in this study are summarized in Table-1. Three of the patients underwent imaging for purposes of staging a malignancy, and one patient underwent imaging for abdominal pain. None of the four patients exhibited preoperative clinical features of catecholamine excess. One patient underwent serologic analysis, which demonstrated normal levels of plasma metanephrine and normetanephrine. Another patient underwent urinary analysis, which demonstrated normal levels of urinary vanillylmandelic acid and normetanephrine. All patients

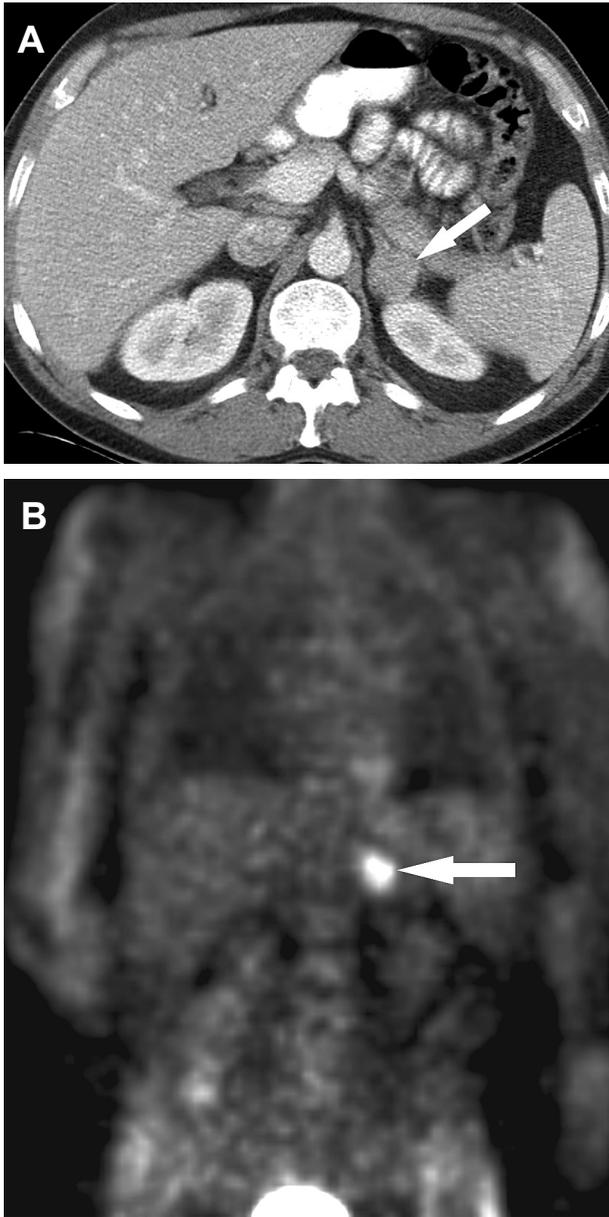
demonstrated an adrenal mass (mean diameter 2.7 cm, range 1.7 to 4.5 cm) with associated heterogeneous (n = 2) or homogeneous (n = 2) enhancement on CT scan. Delayed images obtained in two cases demonstrated less than fifty percent washout. One patient had additional imaging with PET, which demonstrated increased FDG uptake within the lesion. The radiological findings of the four patients are highlighted in Figures-1 to 4. All 4 patients proceeded to adrenalectomy, either open (n = 2) or laparoscopic (n = 2). The intraoperative course of two patients was notable for blood pressure lability peaking at 200/100 to 220/110 mmHg systolic/diastolic. The postoperative course of one of these two patients was complicated by an elevated troponin level to 9.7 and an electrocardiogram consistent with a non Q-wave myocardial infarction.



**Figure 2** – Axial contrast-enhanced portal venous phase CT scan in a 64 year old woman with abdominal pain (Case 2 in Table-1). A heterogeneously enhancing mass (arrow) is seen anterior to the left renal vessels. The left adrenal gland (not shown) was identified just superior to this mass. Open exploratory laparotomy and adrenalectomy was performed, based on a preoperative working diagnosis of retroperitoneal sarcoma. Surgery demonstrated a mass arising exophytically from the inferior aspect of the left adrenal gland, and was complicated by intraoperative hemodynamic instability. The mass was removed expeditiously and final pathology revealed a diagnosis of pheochromocytoma.

## COMMENTS

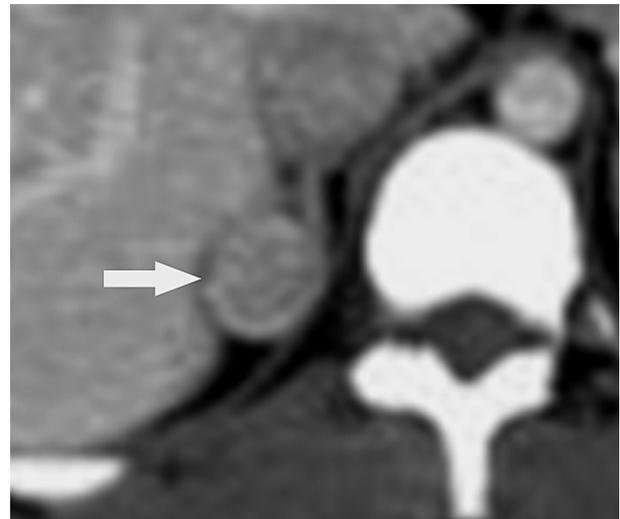
Our study illustrates the importance of keeping a high index of suspicion for the possibility of



**Figure 3** – A) Axial contrast-enhanced portal venous phase CT scan in a 49 year old man with melanoma (Case 3 in Table-1) shows a homogeneously enhancing left adrenal mass (arrow). B) Coronal PET image shows increased fluoro-2-deoxy-D-glucose (FDG) uptake in the mass (arrow). The patient proceeded to laparoscopic adrenalectomy for presumed metastatic disease, with an uneventful intraoperative and postoperative course. Final pathology revealed a diagnosis of pheochromocytoma.

pheochromocytoma for any retroperitoneal mass. While hemodynamic instability associated with surgical and laparoscopic resection of known or suspected pheochromocytoma has been reported (9,10), the risk of resection in the population of unsuspected pheochromocytoma has not been well described to our knowledge. Two out of four of our patients demonstrated intraoperative hemodynamic instability that may have been prevented by appropriate preoperative alpha-blockade. The postoperative morbidity in our population might also have been averted, as the myocardial infarction of one of our patients was presumably related to the sudden intraoperative hypertensive challenge.

Defining typical characteristics of a pheochromocytoma by CT is difficult as heterogeneous enhancement and poor washout as well as FDG uptake on PET may also be seen in a metastasis or adenoma (1,4,11). Further imaging by magnetic resonance (MR) is also problematic, as up to 35% of pheochromocytomas do not exhibit the “lightbulb bright” high T2 signal classically associated with pheochromocytomas (1). Current guidelines on preoperative diagno-



**Figure 4** – Axial contrast-enhanced portal venous phase CT scan in a 25 year old woman undergoing re-staging of Hodgkin’s lymphoma previously treated by chemotherapy and radiotherapy (Case 4 in Table-1) shows a homogeneously enhancing right adrenal mass (arrow). The patient proceeded to laparoscopic adrenalectomy for suspected recurrent lymphoma, with an uneventful intraoperative and postoperative course. Final pathology revealed a diagnosis of pheochromocytoma.

sis thus include additional studies after diagnosis of an adrenal mass with nonspecific characteristics on cross-sectional imaging. Metaiodobenzylguanidine (MIBG) reportedly has an excellent specificity of up to 100% and may increase the sensitivity of pheochromocytoma detection to around 80% (10,12). Given the suboptimal sensitivity of biochemical markers alone, a combination of MIBG imaging supplemented with biochemical testing is currently recommended (12,13). Such an imaging approach may result in better preoperative identification of pheochromocytomas, and facilitate commencement of pre-operative alpha blockade. Both appropriate pretreatment with alpha blockade and readily available intraoperative antihypertensive agents have been shown to decrease intraoperative lability (14). While pretreatment does not exclude the possibility of intraoperative fluctuations in blood pressure (9,10), more favorable blood pressure control may be achieved with a combination of pretreatment and intraoperative medications (15). In a recent series of 24 patients who underwent laparoscopic adrenalectomy for adrenal pheochromocytoma (most were treated pre-operatively with prazosin), no cases of intra-operative hemodynamic instability were reported (16). While such pharmacological blockade may prevent clinically significant hemodynamic changes, it may not prevent biochemical changes. For example, analysis of serial catecholamine levels in 11 patients undergoing 12 laparoscopic adrenalectomies while being maintained on an intravenous alpha 1 blocker showed significant elevations related to the induction of pneumoperitoneum and manipulation of the adrenal gland (17).

Our report has several limitations. The study is a small retrospective case series, and cases were not identified systematically. Patients with enhancing adrenal masses with poor washout or increased FDG uptake at PET imaging undergoing resection were not studied prospectively, and as such, the frequency of pheochromocytoma in adrenal masses with nonspecific imaging characteristics is unknown. Only two out of four patients received screening for catecholamines, and systematic evaluation of the rate of false negatives either by urinary or plasma analysis was therefore not made. Further imaging with MIBG was not obtained in any of our patients, and the rate of false negatives by MIBG was thus not obtained.

In conclusion, we report that two of four patients who underwent resection of unsuspected pheochromocytoma sustained intraoperative hemodynamic instability. This study emphasizes the asymptomatic presentation, nonspecific imaging characteristics, potential for false negative preoperative laboratory analysis, and resultant risk of catecholamine crisis in patients with adrenal masses. Accordingly, both surgeons and radiologists should maintain a high index of suspicion for pheochromocytoma before resection of nonspecific adrenal masses even in asymptomatic patients. Further studies to better delineate the imaging and biochemical preoperative evaluation of these patients are required.

## CONFLICT OF INTEREST

None declared.

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**EDITORIAL COMMENT**

The authors of this paper deserve to be complimented because, despite the modest data, that was analyzed retrospectively, they raise some issues that are very relevant for those who study and treat adrenal diseases.

First of all, they point out that adrenal masses, and I would add retroperitoneal masses in general, can be pheochromocytomas or paragangliomas without clinical signs or with very subtle symptoms, which do

not lead the physician to consider lesions that produce adrenergic substances. In my personal experience (1-3), I had the opportunity to find some pheochromocytomas that had not been diagnosed preoperatively, much like the authors of this paper. Even worse, I found pheochromocytomas that had been diagnosed by endocrinologists as non-functioning, which produced adrenergic discharges in the operating room, causing all of the risks described by the authors.

Secondly, the authors show that any surgeon is likely to encounter a patient that has not been properly diagnosed and reacts to what he believes to be a pheochromocytoma in the beginning of the procedure, causing hemodynamic instability. This creates a dilemma to the surgical team: move forward or abort the procedure? In my personal opinion, the safest measure is to stop the procedure and adequately prepare the patient for another surgery 30 or 45 days later. However, I acknowledge that if the team is very experienced (both surgeons and anesthesiologists), in a hospital with all the necessary resources (medications and support), the procedure can be carried out with good chances of success.

Finally, and this is the main point of my analysis before the facts that were presented by the authors, each case of adrenal mass or retroperitoneal mass suspected of being a pheochromocytoma or a paraganglioma, regardless of the existence of symptoms, must be exhaustively analyzed by an endocrinologist

with expertise in adrenal diseases. Personally, I do not consider myself capable of making such evaluation and I believe that most adrenal surgeons are not. From my own personal experience, I believe that most endocrinologists are not capable of performing this task.

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# Early Removal of Nasogastric Tube is Beneficial for Patients Undergoing Radical Cystectomy with Urinary Diversion

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## ABSTRACT

*Purpose:* Examine the beneficial effect of early nasogastric tube (NGT) removal in patients undergoing radical cystectomy with urinary diversion.

*Patients and Methods:* 43 consecutive patients underwent radical cystectomy with urinary diversion and were randomized into 2 groups. In the intervention group (n = 22), the NGT was removed 12 hours after the operation. Comparatively, in the control group (n = 21), the NGT remained in place until the appearance of the first flatus. The appearance of ileus, patient ambulation, time to regular diet, and hospital discharge of the two patient groups were assessed. Patient discomfort due to the NGT was also recorded.

*Results:* The 2 groups showed statistical homogeneity of their baseline characteristics. Two patients (9.09%) from the intervention and 3 patients (14.3%) from the control group developed postoperative ileus and were treated conservatively. No significant differences in intraoperative, postoperative, bowel outcomes or other complications were found between the two groups. All patients preferred the NGT to be removed first in comparison to their other co-existing drains.

*Conclusions:* This is the first randomized, prospective study, to our knowledge, to assess early NGT removal after radical cystectomy. We advocate early removal, independently of the selected type of urinary diversion, since it is not correlated with ileus and is advantageous in terms of patient comfort and earlier ambulation.

*Key words:* bladder cancer; cystectomy; urinary diversion; nasogastric tube

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## INTRODUCTION

Radical cystectomy with urinary diversion for the management of muscle-invasive bladder cancer, even nowadays, is considered to be an operation that conceals a variety of intraoperative and postoperative hazards. During the last decades, there has nevertheless been an evolution of the surgical experience concerning various techniques. Thus, the risk of complications is much lower, with postoperative ileus being the most common, resulting in prolonged fasting and hospitalization of the patients (1).

A common way to avoid this complication is the use of a nasogastric tube (NGT) which is considered a useful tool that decompresses the intestine and the stomach, increases bowel motility, offering safety to the postoperative care plan. In previous decades, the application of NGTs had become a tradition due to the sense of security it provides to the postoperative outcome. Recently, there have been several prospective randomized trials in the field of general surgery and gynecology supporting the opinion that the benefits outnumber the risks for early NGT removal (2-9). In the last decade there has also been a trend of early

NGT removal after major urologic operations, including radical cystectomy with urinary diversion (10-14). However, a recently published Cochrane Meta-Analysis of 33 studies concluded that NGT decompression should be abandoned in favor of selective use, since it does not accomplish any of its intended goals (15). The purpose of our study was to support this opinion, proving that NGTs can be safely removed shortly after the operation.

**MATERIALS AND METHODS**

Under institutional approval we prospectively evaluated 56 patients from March 2004 to April 2008. Thirteen patients were excluded from the study, 7 due to refusal to participate and 6 patients due to intensive care unit stay, previous history of major abdominal surgery and/or neoadjuvant radiotherapy or chemotherapy. The remaining 43 patients, after providing informed consent, were randomly divided into 2 groups. The intervention and control groups consisted of 22 and 21 patients, respectively. Their demographic

characteristics are listed in Table-1. They underwent radical cystectomy with curative intent for invasive bladder cancer, (30 men and 13 women). The operations were performed by 4 different surgeons.

The perioperative care plan of the two groups is presented in Table-2. The patients of the intervention group followed a common preoperative strategy including admission 2 days before the operation, and counseling regarding the importance of early ambulation and pulmonary physiotherapy compared with the use of NGTs. Bowel preparation was administered the day before the operation, usually with sodium phosphate solution. The night before the operation, a clear liquid diet was administered, and patients received nothing by mouth after midnight. The day of the operation, patients received prophylaxis for deep vein thrombosis including low molecular weight heparin and elastic stockings, as well as chemoprophylaxis usually with intravenous administration of ampicillin and metronidazole. After anesthesia induction a NGT was inserted for bowel and stomach decompression and its correct placement was inspected by the surgeon intraoperatively. We performed an infraumbilical

*Table 1 – Patient demographics.*

	Intervention Group	Control Group	p Value
Total patients (n)	22	21	
Gender (n)			
Male	16	14	
Female	6	7	
Mean age (years ± SD)	66.1 ± 6.73	66.3±4.46	0.932
Type of urinary diversion			0.915
Neobladder	9	9	
Bricker	13	12	
Mean weight (kg ± SD)	78.5 ± 10.77	79.1±15.7	0.886
Mean operation time (hrs ± SD)	4.09 ± 0.79	3.64±0.41	0.026
Mean blood loss (units ± SD)	2.5 ± 1.56	2.61±1.36	0.731
Comorbidities (n)			
None	14	12	
Concurrent malignancy	1	0	
Heart disease	11	14	
Hypertension	3	6	
Diabetes	4	5	
COPD	2	5	

*COPD = chronic obstructive pulmonary disease; SD = standard deviation.*

## Nasogastric Tube and Cystectomy

**Table 2 – Perioperative care plan (POD = postoperative day).**

	Intervention Group	Control Group	p Value
Use of staplers (N)			1.0
Yes	21	16	
No	1	5	
Use of epidural anesthesia			1.0
Yes	3	2	
No	19	19	
Nasogastric tube removal (N)			
12 hrs postoperatively	22	0	
1st POD	0	6	
2nd POD	0	9	
3rd POD	0	5	
4th POD	0	1	
Ambulation (N)			0.289
1st POD	16	12	
2 <sup>nd</sup> POD	6	9	

incision starting just below the umbilical level and extending to the pubic symphysis reaching a maximum length of 12 cm. The operation was performed through an intraperitoneal approach. Removal of the urinary bladder, the prostate, the seminal vesicles and the distal ureters was performed in men, and the bladder with the uterus was performed in women. Bilateral pelvic lymphadenectomy was routinely a part of the operation plan. The urinary diversion was executed with a Bricker ileal conduit (13 patients), or orthotopic bladder substitution (9 patients). The bowel segment that was routinely used was 15-20 cm long, approximately 20 cm away from the ileocecal valve. A longer, ileal loop of 36 cm, formatted accordingly to our personal modification of the S-pouch, was used for the neobladder formation (16). For bowel segment isolation, as well as for restoration of bowel continuity, special staplers were used in most cases. One or two drains were usually applied for postoperative fluid drainage. The simultaneous use of an epidural is not common in postoperative analgesia. Postoperative pain was managed with systemic use of opioids and nonsteroidal anti-inflammatory drugs. Metoclopramide was routinely used in all cases for 48 hours postoperatively. The NGT was removed within 12 hrs postoperatively. Ambulation with respiratory physiotherapy if needed was usually

begun on the first postoperative day along with a clear liquid diet, whereas the patients had their first regular meal after 3 to 4 days. This postoperative care plan was applied irrespectively of the presence of flatus or bowel sounds. Postoperative ileus was defined as the absence of normal flatus or stool for 5 days with accompanying symptoms like nausea, vomiting, gas distention, and confirmation with imaging parameters. The criteria for safe discharge included adequate oral intake, pain control with oral medication and defecation accomplishment. All of the patients that suffered from ileus were treated conservatively with reinsertion of the NGT and modification of the diet.

The 21 patients of the control group were operated on during the same period of time by the same group of surgeons and with identical surgical techniques. Urinary diversion was executed with a Bricker ileal conduit (9 patients) and orthotopic bladder substitution (12 patients). The preoperative plan was identical to those of the intervention group. Postoperatively, the only difference was that the NGT remained until the appearance of the first flatus.

The patients were asked a simple question 12 hours postoperatively about which “tube” (catheter, drain, NGT) they would prefer to be removed first due to its discomfort.

Statistical “homogeneity” of the two patient groups was explored using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson’s chi-square test was used to examine the “relationship” between the time of NGT removal and the operative techniques (type of operation, use of staplers). The use of epidural anesthesia was examined using the Fisher’s exact test. We also performed the parametric test (independent samples t-test) to compare the (mean) operation time with a 95% confidence interval. Finally, the Mann-Whitney U test was used to examine the surgical outcomes.

## RESULTS

No statistical difference was found in any demographic or clinical parameter between the 2 groups. No patients were lost to follow-up during the intervention, nor discontinued the intervention. Likewise, no difference was recorded in the postoperative course, especially concerning bowel movement, ambulation or patient diet. The main results are listed in Tables 2 and 3.

The only parameter which showed a statistically significant difference was the mean operative time ( $p = 0.026$ ). Complications (Table-3) were rare and comparable between the two groups ( $p = 0.69$ ).

Concerning the tube removal question, all patients (100%) answered that they would prefer the NGT to be removed first.

## COMMENTS

The 90-day morbidity and mortality rates for radical cystectomy have been reported to reach the non-negligible rates of 64% (17) and 5.6% (18). This is the main reason why many urologists prefer being more conservative in their postoperative treatment plan. A major postoperative concern is related to postoperative ileus. In many cases, to avoid this complication, a NGT remains in place for several days after the operation. The preservation of the NGT for more than one day though, is associated with patient discomfort, increased pulmonary complications like atelectasis and respiratory tract infections, gastro-

esophageal reflux and electrolyte imbalances (10). Early patient ambulation has been traditionally encouraged to stimulate the bowel and prevent respiratory events, but despite the strong clinical bias, it seems to have little or no effect on NGT removal (11).

There have been alternative methods used for gastrointestinal (GI) tract decompression. Some centers have tested the use of tube gastrostomy with positive results [19-22]. In 1976, the first trial comparing tube gastrostomies and NGTs was published concluding that gastrostomies have a definite place in surgical urology (19). Fifteen years later, Van Poppel et al. reported that tube gastrostomies can be an easy procedure for gastric decompression after urinary diversion procedures but can be used only as an alternative to NGTs (20). Finally in 2000, Buscarini et al. presented a clinical trial with 709 patients, suggesting the tube gastrostomy with the Stamm technique as an effective method with a low complication rate (0.05%) (22). Currently, this technique is not so popular among urologists due to its high level of invasiveness and the reduced need for long lasting gastric decompression.

Early NGT removal has been a matter of controversy. In 1999, Donat et al. presented the first prospective study comparing 27 patients receiving intravenous metoclopramide combined with NGT removal before 24 hours, with 54 control patients. Their results focused on the importance of metoclopramide with early NGT removal in the reduction of postoperative atelectasis, early return of bowel function, and safety to the small bowel anastomosis (10). In 2003, Pruthi et al. with a relatively small sample of patients, was the first to focus on a specific preoperative plan with bowel preparation and patient education, combined with a limited incision length, preperitoneal approach, use of staplers, and early NGT removal, in the early hospital discharge of their patients (12). Inman et al. during the same year, with a large sample of 430 patients, retrospectively compared patients who received postoperative NGTs with those who did not, suggesting that NGTs may prolong GI recovery and increase duration of hospitalization (13). Finally, in 2005, Park et al. pointed out the importance of sodium phosphate for bowel preparation in the reduction of the incidence of postoperative ileus and supported the opinion that early NGT removal after cystectomy is not related with ileus (14). Other authors propose the

Table 3 – Outcomes.

	Intervention Group	Control Group	p Value
1 <sup>st</sup> bowel sound (N)			0.898
1 <sup>st</sup> POD	9	9	
2 <sup>nd</sup> POD	10	8	
3 <sup>rd</sup> POD	3	3	
4 <sup>th</sup> POD		1	
1 <sup>st</sup> flatus (N)			0.955
1 <sup>st</sup> POD	2	1	
2 <sup>nd</sup> POD	13	14	
3 <sup>rd</sup> POD	4	4	
4 <sup>th</sup> POD	3	2	
Mean time to regular diet (days ± SD)	3.45 ± 0.9	3.43 ± 0.74	0.203
1 <sup>st</sup> defecation (days ± SD)	4.77 ± 1.19	4.33 ± 1.06	0.14
Hospital discharge (days ± SD)	12.6 ± 3.4	12.43 ± 2.71	0.686
Complications (N)		NS	0.69
None	24	26	
Flatulence	2	-	
Ileus	2	3	
Urine leakage from drainage tube	-	2	
Cardiac failure	2	-	
Fever	3	4	
Wound disruption	-	1	
None	19	22	
Ileus	2	3	
Urine leakage from drainage tube	0	2	
Cardiac failure	2	0	
Fever	2	2	

SD = standard deviation.

use of chewing gum for bowel motility stimulation (23).

Postoperative ileus is associated with pre-, intra- and postoperative factors, such as prolonged fasting, the surgical stress along with the sympathetic hyperactivity, uncontrolled pain, hypotension, hypovolemia, surgical dissection and excessive saline administration. We tried to avoid all of the above factors, in cooperation with our anesthesiologists, by creating a careful prospective, preoperative and postoperative care plan, incorporating respective measures.

Preoperatively, we carried-out a meticulous counseling effort to stress the importance of bowel preparation, early ambulation and pulmonary exercise. Sodium phosphate solutions fulfill the criteria

regarding tolerability, adequate preparation of the ileum and reduced morbidity. Even though patients do not benefit from bowel preparation, as a recent meta-analysis in major abdominal surgery suggests (24), we proceeded to use a one-day bowel preparation. Nevertheless, we do not consider bowel preparation as an important factor in the preoperative preparation of the patient. Furthermore, we do not advocate prolonged fasting, because it leads to insulin resistance and it is not recommended by international anesthesiology guidelines (25). Moreover, gastric emptying of water and other clear fluids has an extremely fast exponential curve (50% of intake clearance within 20 minutes) (26). The preoperative care plan rarely included chemoprophylaxis from the previous day

because of the small bowel segment used in most of the cases. In this instance, possible postoperative complications like ileus or superinfection by *Clostridium difficile* resulting in pseudomembranous colitis can be avoided (27).

Intraoperatively, performing radical cystectomy through a limited infraumbilical incision not exceeding 12 cm provided us with several benefits. The bowel loops do not block the surgical field and are better protected inside the abdomen due to the smaller incision of the peritoneum. Finally, the postoperative pain is limited with this type of incision. The use of staplers during all of the stages of the operation offers less operating time, reduced intraoperative blood loss, and improved bowel manipulation (28). In this case, the risk of postoperative bowel edema and ileus is greatly reduced and the early induction of a normal diet is facilitated.

Of the 43 patients, only 5 had GI tract complications. These complications occurred with no significant difference between the two groups, they were not related with increased estimated blood loss, transfusion requirement, or other major complications like fever.

This study is not without limitations. Firstly, our patient sample is rather small, but it is homogeneous. Second, our patients were operated on by 4 different surgeons creating a possible bias. However, the technique used by all surgeons in our department was exactly the same, although it might have created a difference in operative time. Additionally, the tube removal question is rather simple, not subjective, but it does reflect the patient's discomfort accurately. Finally, it is obvious that this study did not follow the multimodal approach of the fast track program (no mechanical bowel preparation, no drainages, epidural analgesia, etc.), but it was done in order to focus entirely on the effects of NGT in the postoperative course of the patient.

To our knowledge, this is the first randomized, prospective trial evaluating the value of early NGT removal in a radical cystectomy with urinary diversion. We believe that NGT does not affect bowel movement and does not prevent prolonged postoperative ileus. Our results are in accordance to the current literature that reducing time to NGT removal can be advantageous in terms of patient comfort.

## CONFLICT OF INTEREST

None declared.

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# Invasive Bladder Cancer in the Eighties: Transurethral Resection or Cystectomy?

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## ABSTRACT

*Purpose:* Describe morbidity and survival in patients older than 80 years with muscle invasive bladder cancer (MIBC) treated with radical cystectomy (RC) or transurethral resection (TUR) in our institution.

*Materials and Methods:* We reviewed our database of all patients older than 80 years treated with RC and TUR for MIBC between 1993 and 2005 in our institution. Twenty-seven patients were submitted to RC, with mean age of 82 years and mean follow-up of 16.4 months. RC was carried out following diagnosis of previous MIBC in 14 cases (51.9%). The American Society of Anesthesiology (ASA) score was III or IV in 23 patients (85.1%). Seventy-two patients with a mean age of 84 years and mean follow-up of 33 months, diagnosed with MIBC, were managed by means of TUR. The ASA score was III-IV in 64 (88.8%) patients.

*Results:* Pathological stage of the RC specimen was pT3 in 18 cases (66.7%). Mean hospital stay was 16 days. Early complications were assessed in 8 patients (29.6%), with an overall survival (OS) of 42.94%, and cancer-specific survival (CSS) of 60.54%. In patients submitted to TUR, clinical stage was T2 in 36 cases (50%). The mean hospital stay was 7 days, with a readmission rate (RR) of 87.5%. OS and CSS was less than 20%.

*Conclusions:* RC in octogenarian patients is a safe procedure, with complication and survival rates comparable to RC series in general population. Transurethral resection (TUR) for patients with MIBC within this age range is a much less morbid procedure, but disease specific survival is lower.

*Key words:* urinary bladder neoplasms; cystectomy; endoscopy; aged

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## INTRODUCTION

The increased incidence and prevalence of genitourinary neoplasias over the last few decades can be attributed to demographic evolution and increased life expectancy. The National Cancer Institute has estimated that 89% of the bladder tumors are found in patients older than 55, and that the mean age at diagnosis, is 73 years(1).

Standard treatment for muscle invasive bladder cancer (MIBC) is radical cystectomy with

bilateral pelvic lymphadenectomy, and is justified in patients with life expectancy greater than two years.

In patients more than 80 years old radical surgery tends to be avoided, since is believed to be associated with increased morbidity and mortality rates. Historically those patients have been treated with TUR that is a less aggressive procedure. It is now accepted that the American Society of Anesthesiology (ASA) score for patients undergoing a major procedure is a predictive factor for morbidity and mortality which is more significant than age alone (2). For the last seven

years we have actively performed radical cystectomy (RC) in patients of advanced age with an ASA score compatible with this type of surgery.

## MATERIALS AND METHODS

We reviewed our database of all patients that were treated with either RC or TUR between 1993 and 2005 for invasive bladder cancer and age over 80 that did not receive neoadjuvant or adjuvant therapy.

### Radical Surgery

Twenty-seven patients over 80 years with MIBC were submitted to RC and urinary diversion at our institution between 1993 and 2005. Twenty-two (81.5%) were males and 5 (18.5%) females with mean age  $82 \pm 3$  years (range 80 - 91 years). Inclusion criteria for the patients were detailed medical history, a physical examination, cardiovascular and pulmonary parameters including their metabolic and nutritional status. Indications of RC were based on finding MIBC in TUR, or recurrent high-grade superficial tumors unresponsive to Bacillus Calmette-Guerin (BCG) therapy. Before surgery all patients were staged according to the ASA score (3).

Following surgery patients were monitored at the post-operative care unit during 24 hours. Ureteral catheters were removed 7-10 days following cystectomy.

### Transurethral Resection

A total of 72 patients (59 males and 13 females) over 80 years old were staged for MIBC and suitable for TUR. All cases were staged with bimanual examination under anesthesia and underwent TUR (complete or palliative). Multiple random biopsies were taken to document presence of carcinoma in situ. Follow-up consisted of cystoscopy and TUR if recurrence and/or progression occurred. During follow-up, the numbers of re-admittance and health state of the patients were considered to evaluate the progression of the disease.

Peri-operative mortality was defined as all-cause death up to 30 days after surgery. The overall mortality rate included cancer-related or cancer-unrelated deaths. The morbidity rate included early complications considered adverse effects in the course of hospitalization or 30 days post-surgery and late complications longer than 30 days post-surgery.

## RESULTS

### Cystectomy

Pathology of radical cystectomy (RC) revealed urothelial carcinoma in 26 of the 27 patients (96.3%). Stage was pT3 in 18 cases (66.7%) and association with prostate carcinoma was found in 10 cases (37%) (Table-1).

Urinary diversion was ileal conduit in 24 (88.8%) patients, cutaneous diversion in two patients (7.40%) and Studer orthotopic substitution in one patient (3.80%).

Concomitant cardiovascular disease was the most frequent co-morbidity, with hypertension in 10 patients (37%), previous acute myocardial infarction in 3 patients (11.1%) and arrhythmia in 2 patients (7.4%). Other concomitant pathologies were diabetes mellitus in 4 patients (14.8%), bronchial asthma in 1 patient (3.7%) and emphysema in 3 patients (11.1%).

Intra- or post-operative blood transfusion was necessary in 10 patients (37%); furthermore there were two cases (7.4%) of intraoperative mortality. Early complications occurred in 8 patients (29.6%) and were paralytic ileus in 4 patients, wound infection in 3, intra-abdominal abscess in 1 patient and entero-cutaneous fistula in another one. The major complications were: acute myocardial infarction in one patient and another patient require re-operation due to bleeding.

The mean hospital stay was 16 days (8-28) and the mean follow-up of these patients was 16.4 months (1.4-84.2 months).

Distant disease was found in 8 patients during follow-up: four of those diseases involved lymph nodes and 4 were multiple.

**Table 1– Patient characteristics.**

Patient Characteristics		Cystectomy (%)	TUR (%)
Number of patients		27	72
Sex	Male	22	59
	Female	5	13
ASA (%)	II	4 (14.8)	0
	III	19 (70.4)	20 (27.7)
	IV	4 (14.8)	44 (61.1)
	pT0	2 (7.4)	
Stage (%)	pT2/cT2	3 (11.1)	36 (50)
	cT2-T3		24 (33.3)
	pT3/cT3	18 (66.7)	10 (13.9)
	pT4/cT4	4 (14.8)	2 (2.8)
	Squamous	1 (3.7)	
	Prostate cancer associated	10 (37)	

*ASA = American Society of Anesthesiology score; TUR = transurethral resection.*

Overall survival (OS) was 42.94% and cancer specific survival (CSS) 60.54 % (Table-2, Figure-1).

had died due to other causes, and 7 (9.7%) were lost to follow-up.

### Transurethral Resection

In patients submitted to TUR, the stage was cT2 in 36 cases (50%), cT3 in 10 cases (13.9%), cT2-T3 in 24 cases (33.3%), and cT4 in 2 cases (2.8%). Grade was G3 in 49 cases (68%). Forty-nine patients (68%) had a complete TUR, whereas in 32% resection was incomplete (Table-1).

Intra- or post-operative blood transfusion was necessary in 10 patients (13.8%), and there was no case of intra-operative death. Regarding early complications, hemostatic intervention was required in 6 patients (8.3%), and 2 patients showed manifestations of hemodynamic angina that required intensive care. The mean hospital stay was 7 days; with a readmission rate of 87.5% (thirty patients had 1 readmission, 11 patients had 2 readmissions and 11 patients had 3 or more readmissions). The mean follow-up was 19 months with an overall and CSS of less than 20% (Table-2, Figure-2).

At the end of the follow-up, 8 patients (11%) were alive, 47 (65%) had died due to cancer, 7 (9.7%)

### COMMENTS

In the past, advanced age was a contraindication for cystectomy; some studies reported peri-operative mortality rates of 5.5% in patients younger than 60, versus 11% in patients between 60 and 70 years old (4). Improvements in the surgical technique, anesthetic management and post-operative care have brought a reduction of major complications from an initial 51% down to the current 10-30%, and the mortality rate subsequent to surgery has decreased to 2% (5), with transfusion, hospital stay, early and late complications and survival rates comparable to those of patients younger than 65 years. Moreover, patients presenting with an ASA score compatible with a major intervention are eligible for cystectomy because when it is compatible with major procedures, it reflects the functional status of a patient more accurately than age itself (2,3).

Fifteen years ago, at our institution we only performed TUR. Later we started doing RC throughout the eighties, with two main objectives: improve

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local control disease with better oncological outcomes and minimize complications.

Regarding local control disease, the proportion of patients with advanced pathological stage

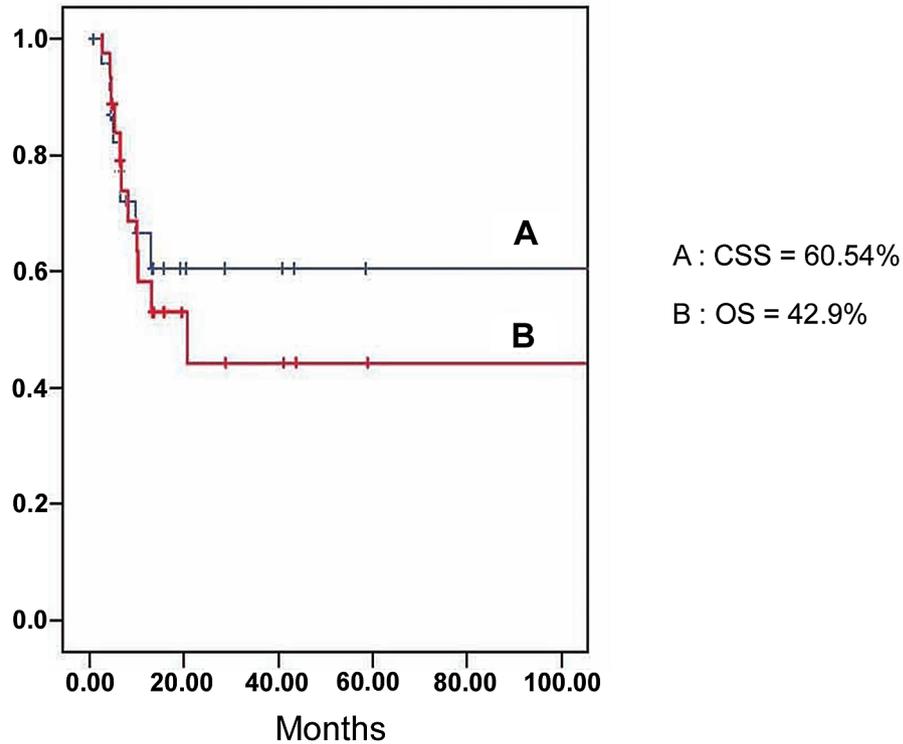


Figure 1 – Survival rates in radical cystectomy patients: A) Cancer-specific survival (CSS), B) Overall survival (OS).

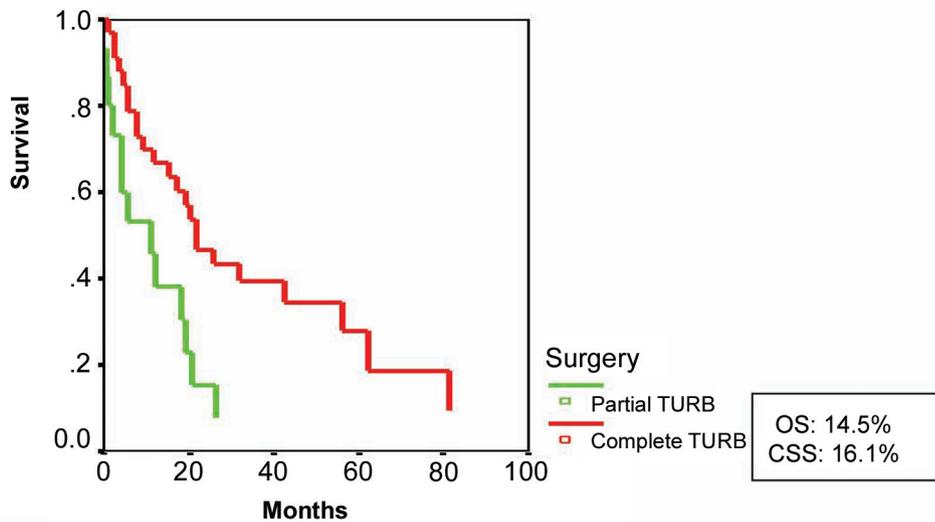


Figure 2 – Survival rates after partial or complete transurethral resection of bladder tumor (TURBT).

**Table 2** – Complications rate and oncological outcomes in RC and TUR.

	Cystectomy	TUR
Global complications rate (%)	33.2	11.1
Transfusion (%)	37	13.8
Follow-up (months)	19	16.4
Overall survival (%)	42.9	14.5
Cancer specific survival (%)	60.5	16.1
Readmission (%)	42	87.5

*RC = radical cystectomy; TUR = transurethral resection.*

in our series was the highest one of all the series reviewed (81.48%) (6-8); supporting the RC indication, since application of conservative alternatives (TUR) would yield a much poorer tumor control. Moreover, our 42.94% OS rate is similar to pT3 series published in younger population (9,10) and the difference in elderly patient data, is because of a shorter follow-up. As to the CSS rate we obtained 60.54% and observed important differences at each stage. If we compare patients with pathologic stage pT2 to the rest of grouped stages, at our follow-up period, all of the pT2 patients continue to be alive, whereas survival of the rest of groups was 55.48%. Most series reviewed report CSS rates between 62% and 84% (11-14) and no significant differences regarding OS or CSS were found in the series reviewed between patients younger and older than 70 years for RC (15,16).

Comparing these results with transurethral resection of bladder tumor (TURBT) for MIBC, good results are shown in case of small T2 tumors (17,18). Our survival rate is below 20%, but we are dealing with not-selected patients with large tumor volumes (32% of them received only palliative TUR). At the end of the follow-up, only 8 patients (11%) were alive and the OS rate was lower than 20% independently of the TUR being complete or partial (Figure-2). Therefore, compared to RC for this age group and with a similar follow-up, even if it is not a prospective and randomized study; overall and cancer-specific survivals are much more favorable for RC.

Regarding complications, intra-operative mortality in our series show two cases (7.40%),

whereas most studies reviewed, show rates between 0% and 7.40%. The published series comparing intra operative mortality among patients younger and older than 70 shown no significant differences between both groups (15). Therefore, peri-operative mortality in the published RC series, some of them with 30 years of follow-up and with 1,359 patients with a mean 67 years of age, was only 2% (19); in this period the primary causes of mortality were those due to cardiovascular decompensation, sepsis frequently related to urinary or bowel fistula, pulmonary embolism and massive postoperative hemorrhage. In case of TUR we do not have any cases of intraoperative or perioperative mortality. The most frequent intraoperative complications were hemorrhage that was responsible for re-intervention in 84% of cases, perforation in 1.3% with incidence that is variable in the various series consulted (2.5-5%) (20) and TUR syndrome.

Ten patients (37%) required either intra- or post-operative blood transfusion, and the mean of transfused units was two (1-3). If differences between the mean units transfused and bleeding in patients younger and older than 70 are compared, significant differences between both groups regarding the mean bleeding in mL and in the number of transfused patients are found, even though transfused patients are larger in number in the older-than-70 group (9). In case of our TUR series, transfusion was necessary in 10 patients (13.8%) that is lower compared with the RC group, but higher if it is compared with our global transfusion rate in TUR that is 3.4% (21).

The mean hospitalization stay of our patients in the group of RC was 16 days (range 8-28). Hospital stay varies between 7-34 days, and in our experience prolongation of hospital stay in patients older than 80 is related with the more difficult solution of their major complications. Moreover, patients with a poor ASA score will potentially be at greater risk of urinary derivation-related post-operative fistulae (2). In our series, the only patient that developed an entero-cutaneous fistula in the postoperative period had an ASA score of III.

TUR group reflect a mean hospitalization stay of seven days that is much better than the RC group, related to the lower impact of the endoscopic surgery for the patient. The problem with this group is a readmission rate that was 87%, related in most cases with hematuria in the context of tumor persistence.

The evaluation of the risk-benefit ratio of the radio-chemotherapy protocols in this cohort of patients over 80 with co-morbidities avoided their use. Available meta-analysis of randomized trials on cisplatin-containing combination neoadjuvant chemotherapy revealed a 5% difference in favor of neoadjuvant chemotherapy, and no randomized trials have yet compared survival with TURBT alone versus cystectomy for the management of patients with muscle-invasive disease, moreover collaborative international adjuvant chemotherapy trials are needed to assist researchers in assessing the true value of adjuvant chemotherapy (22).

Limitation of this study is that it was a descriptive, and not a comparative analysis of two independent series of patients. Further prospective randomized trials are necessary to confirm these findings.

## CONCLUSIONS

RC in octogenarian patients is a safe procedure, with complication and survival rates comparable to those of the series of patients younger than 80, and therefore we consider that age is not a contraindication of surgery if it is not accompanied by an unfavorable ASA score.

TUR for patients with MIBC within this age range is a much less morbid procedure, but disease specific survival is lower.

## CONFLICT OF INTEREST

None declared.

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**EDITORIAL COMMENT**

In the present manuscript, the authors compare the cancer specific outcomes of transurethral resection (TUR) versus radical cystectomy in octogenarians with muscle invasive bladder cancer. The authors address an interesting clinical question in a cohort we have traditionally associated to be at increased risk of perioperative complications with aggressive surgical

intervention. The authors conclude appropriately that patients underlying (pre-treatment) co-morbidities (measured using ASA score) is more of a determinant of surgical risk than age alone. Similarly, the authors conclude that radical cystectomy offers an improved cancer specific survival (versus TUR) at the cost of increased perioperative morbidity. I would argue that

TUR alone (without consideration of a bladder sparing type approach using chemo-radiotherapy or at the very least of adjuvant radiotherapy to the bladder and pelvic lymph nodes for local/regional cancer control) is not an oncologic efficacious treatment alternative except in the very rare case of a patient with a focally muscle invasive bladder tumor. Hence, the importance of repeat TUR (to ensure complete resection), random bladder biopsies (to rule out multifocal disease), and exam under anesthesia (to adequately assess clinical stage) should be considered essential in these select patients treated by TUR alone. Similarly, careful pathologic review of the TUR specimen by an experi-

enced genitourinary pathologist is essential to confirm tumor invasion into the muscularis propria and rule out the presence of adverse pathological features such as lymphovascular invasion or micropapillary histology.

In summary, there clearly remains a subset of patients with muscle invasive bladder cancer for whom cystectomy is not a feasible choice because of pre-operative co-morbidities or by their refusal to proceed with aggressive surgical intervention. In these patients, clinicians must tailor their treatment options based on patient and tumor specific characteristics.

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# Parallel Determination of NeuroD1, Chromogranin-A, KI67 and Androgen Receptor Expression in Surgically Treated Prostate Cancers

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## ABSTRACT

**Purpose:** Neuroendocrine differentiation is a hallmark of prostate cancer. The aim of our study was the detection of the parallel expression of neuroendocrine related markers using a prostate tissue microarray (TMA).

**Materials and Methods:** Our study was aimed at detecting the parallel expression of NeuroD1, Chromogranin-A (ChrA), Androgen Receptor (AR) and Ki-67 by immunohistochemistry on prostate cancer tissue microarray. The data was analyzed using SAS version 8.2 (SAS Inc, Cary, NC). The relationships between NeuroD1, ChrA and AR expressions and patients' characteristics were investigated by multivariate logistic regression analysis. Progression and Overall Survival (OS) distributions were calculated using Kaplan-Meier method.

**Results:** Tissue reactivity for NeuroD1, ChrA and AR concerned 73%, 49% and 77% of the available cases, respectively. Regarding overall survival, there were 87 deaths and 295 patients alive/censored (6 years of median follow-up). Seventy-seven disease progressions occurred at the median follow-up 5.4y. A significant correlation between NeuroD1, ChrA and AR expression was observed ( $p < 0.001$  and  $p < 0.03$ , respectively). Additionally, ChrA was strongly associated in multivariate analysis to Gleason score and Ki67 expression ( $p < 0.009$  and  $p < 0.0052$ , respectively). Survival analysis showed no association between markers neither for overall nor for cancer-specific survival.

**Conclusions:** The results highlight that NeuroD1, Chromogranin-A and Androgen Receptor are strongly associated, however their expression does not correlate with overall survival or disease progression.

**Key words:** prostatic neoplasms; neuroendocrine cells; neuroD1 protein; ki-67 antigen; chromogranin A, receptors, androgen prognosis

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## INTRODUCTION

Prostate cancer (PCa) is the most frequent cancer in Western countries and the second leading

cause of cancer related deaths in men (1,2). The clinical course of this cancer is often unfavorable due to the shift from androgen dependent status to hormone refractoriness. The change in clinical course correlates

with a strong increase in biological aggressiveness and a significant decrease in survival (3). Only a few studies on docetaxel-based chemotherapy have reported results in terms of survival, pain control, quality of life and progression in patients with metastatic castration-resistant prostate cancer (CRPC) (4,5), albeit the risk of cytotoxic chemotherapy should be individually weighted.

In recent years, the presence of neuroendocrine differentiation (NED) features has been reported as a variable associated with the development of the CRPC (6,7) during the natural history of this PCa. In general, pure neuroendocrine (NE) tumor cells do not express androgen receptors (AR), are resistant to androgen deprivation therapy and do not proliferate in response to androgens (8). Autocrine-paracrine epithelial interactions and/or transdifferentiation are the mechanisms through which NE cells act in PCa homeostasis (9).

The early detection of NE activity in prostate adenocarcinoma could suggest or anticipate an early diagnosis of hormones refractoriness behavior and thus justify changes in therapeutic approaches. Unfortunately, the diagnosis and the quantification of prostatic NE cell activity remains a problem. Chromogranin A (ChrA), consistently expressed during NE cell differentiation (8), is the most frequently used marker to detect NE differentiation in PCa patients, both at tissue and at serum level (10,11). Nevertheless, differences between assays for serum ChrA provided a significant discordance rate, suggesting that the commercial kits for serum detection might elicit different information (12). Moreover, tissue ChrA lack prognostic significance in patients with bone metastatic PCa (13). Other NE markers (such as tissue CD56, synaptophysin) add only little information on the acquisition of NE phenotype in human prostate (14). Neuron-specific enolase (NSE) could become a valuable tumor progression marker and could serve as predictor of survival together with clinical parameters but only in advanced and hormone refractory prostate neoplasms (15,16).

These evidences highlight that the identification of new diagnostic and prognostic markers is relevant for the clinical management of PCa patients, especially related to neuroendocrine differentiation. Following the identification of the neurogenic char-

acteristic of the 2q31-33 genome region (HOX D locus) which houses genes involved with epithelial-neuronal cell conversion (17), we investigated the role of NeuroD1 in normal and neoplastic human prostates. We have previously reported that NeuroD1 tissue reactivity correlates with the indicators of malignancy in moderately to poorly differentiated PCa and it could be involved in the pathophysiology of PCa neuroendocrine differentiation (14). Here we report on an immunohistochemical analysis using a tissue micro array (TMA) containing a high number of different naive prostate cancer specimens, in order to verify the prognostic relevance of NeuroD1 together with ChrA, AR and Ki67 tissue reactivity and their correlations.

## MATERIALS AND METHODS

A total of 732 patients (members of the Kaiser Foundation Health Plan) treated for clinically localized PCa by radical prostatectomy or transurethral resection (TURP) (incidental diagnosis) at one of two Kaiser Hospitals in Portland (OR, USA) between 1971 and 1996, were retrospectively evaluated. The full study protocol, including access to the slides and blocks, was reviewed and approved by the Committee for the Protection of Human Subjects of Kaiser Permanente, Portland, OR. All patient identifiers were removed and replaced by unique study numbers, linked to the original identifiers by a single file kept under high security. Medical records for the entire cohort were abstracted at one time, 1999-2001, to assure uniform criteria for diagnosis, progression, and staging.

Selection of the specimens, classification, as well as patient management and follow-up have extensively been described elsewhere (18). Before 1992 (pre-PSA era), progression was defined clinically based on the results of bone scans, chest x-rays, and/or digital rectal examination. After 1992, progression was defined by increasing PSA serum concentrations in serial determinations following a postoperative PSA nadir value (18). Patients with N+ or M+ disease at the diagnosis or treated by neoadjuvant or postoperative hormonal or chemotherapy have been excluded.

Benign prostatic hyperplasia (BPH), as control, was also evaluated in 89 specimens (not included in the analysis).

### Tissue Microarray Design

The prostate TMA was constructed as previously described (18,19). Briefly, one core tissue-biopsy (diameter 0.6 mm) was taken from the least differentiated region of individual paraffin-embedded prostate tumors (donor blocks) and precisely arrayed into a new recipient paraffin block (35-20 mm) with a custom-built precision instrument (Beecher Instruments, Silver Spring, MD). The core-tissue biopsies were put into one of the two recipient blocks that defined one replicate TMA. Six replicate TMAs containing the identical set of tumors were constructed. After the block construction, 5 mm sections were cut using a microtome. Originally, 732 donor tissue blocks were available for the construction of this TMA. Specimens from 74 tumors could not be included in the study because of incomplete follow-up data, lack of tumor in the arrayed sample (sampling error), damaged tissue (heat or crush artifacts), or a total lack of tissue at some array positions ('empty spots'). The number of patients varies between the individual marker analyses because of variability in the number of interpretable specimens on consecutive sections.

The presence of tumor tissue on the arrayed samples was verified on a hematoxylin-eosin-stained section. All data in this study are based upon the analysis of 658 PCa specimens.

### Immunohistochemistry

Sections (4  $\mu$ m) of TMA blocks were transferred to an adhesive-coated slide system (Instrumedics Inc, Hackensack, NJ, USA). After incubation, immunodetection was performed following a standard avidin-biotin complex method (LSAB-DAKO; Glostrup, Denmark, and DAB; Vector Laboratories, Burlingame, CA.). The slides were immunoassayed for neuroD1 (sc-20805, 1:150; Santa Cruz Biotechnology, Santa Cruz, CA.), Ki-67 (MIB1, 1:800; Dako, Glostrup, Denmark), chromogranin A (DAK-A3,

1:100; Dako, Milan, Italy) and androgen receptor (clone AR 441 1:300 DAKO, Glostrup, Denmark).

Stained TMA sections were evaluated by pathologists using uniform criteria. In particular, single markers expression was recorded as negative/positive, considering expression in normal versus neoplastic, being the discrepancies resolved in a reviewed joint analysis.

The fraction of immunohistochemically positive cells per punch was evaluated. NeuroD1 was classified as 0%, 1-50%, > 50%. Chromogranin A was classified as 0-4%, 5-9%,  $\geq$  10%. For Ki67 and androgen receptor, only nuclear staining was considered. AR was classified as 0-10%, 11-50%, > 50%; whereas Ki67 was visually scored and stratified into two groups (low  $\leq$  10%; high > 10%) (18). The cut-off values used in the analyses have been selected on the bases of the best possible discriminatory effect.

### Statistical Analysis

The data was analyzed using SAS version 8.2 (SAS Inc, Cary, NC). A two-tailed P value < 0.05 was considered significant. Continuous variables were expressed as mean and Standard Deviation and compared with ANOVA. Categorical variables were expressed as a number or a percentage and compared by using Fisher's exact test. The relationships between NeuroD1, ChrA and AR expressions and patients' characteristics were investigated by multivariate logistic regression analysis. Progression and Overall Survival (OS) distributions were calculated using the Kaplan-Meier method.

## RESULTS

The main clinical-pathological characteristics of the biopsies are listed in Table-1. Follow-up data for progression (median 5.4, range 0.5-20 years) were available in 631 cases. For the overall survival were useful data from 623 patients (median 6, range 2-20 years). Gleason score was assessed for all the PCa specimens on TMA (658 punches) and classified as well, moderately, or poorly differentiated (Gleason score < 7, 7, > 7, respectively). The Gleason score and

**Table 1** – Main clinical and pathological findings of 658 patients.

Characteristics	N (%)*
Median age (range), years	65 (45-92)
Surgery	
RP	589 (89)
TURP	71 (11)
Gleason score	
<7	378 (57.5)
7	224 (34.0)
>7	56 (8.5)
Stage	
pT2	467 (71.0)
pT3	105 (16.0)
pT4	27 (4.1)
pTx	59 (9.0)
High Grade PIN	25 (3.8)
Perineural invasion	270 (41.0)
Seminal vesicles invasion	35 (5.3)
Urethral invasion	42 (6.4)
NeuroD1	
Absent	107 (26.2)
Intermediate	130 (31.8)
High	172 (42.1)
ChrA	
Low	358 (57.0)
Intermediate	165 (26.3)
High	105 (16.7)
AR	
Low	142 (38.1)
Intermediate	131 (35.1)
High	100 (26.8)
Ki67	
Low	459 (85.5)
High	78 (14.5)

\*tables entries are absolute numbers and percentages, but for age. RP = Radical Prostatectomy; TURP = Transurethral resection; PIN = Prostatic intraepithelial neoplasia; ChrA = chromogranin-A; AR = androgen receptor; Ki67 = Ki67 label index.

pathologic stage were highly predictive for progression ( $p < 0.0001$ ) and overall survival ( $p < 0.0001$ ).

## Immunohistochemistry

A total of 409 PCa punches were available to detect for NeuroD1 protein expression. Among these, 302 (73%) showed a NeuroD1 positive cytoplasmic staining (Table-1). Only few cases showed a faint nuclear stain. Results according to Gleason score were reported in Table-2. NeuroD1 expression has shown significant association with ChrA ( $p < 0.001$ ) and AR expression ( $p < 0.004$ ) (Table-3). Only 3/89 (3%) cases of BPH showed a weak positivity. Failure of analysis occurred in 249 cases mostly for unreliability of staining or missing/damaged tissue.

Of 628 PCa punches valuable for ChrA expression, 270 (43%) showed a moderately-to-high positive staining (Table-1). For ChrA, 30 cases are invaluable or missing tissue, due to technical problems. The immunohistochemical analysis revealed a cytoplasmic positivity, whereas 206 cases were completely negative. Twenty cases of BPH were focally positive. Results according to Gleason score are reported in Table-3. ChrA expression is associated with Gleason score, NeuroD1, AR and Ki67 index ( $p = 0.002$ ,  $p < 0.001$ ,  $p = 0.004$  and  $p < 0.001$ , respectively) (Tables 2 and 3).

The staining for the AR was available for 373 punches of PCa (Table-1), displaying predominantly a nuclear localization. We detected a low, intermediate and high AR tissue reactivity in 38%, 35% and 27%, respectively. AR expression is associated with NeuroD1 and ChrA ( $p = 0.004$  and  $p = 0.004$ , respectively).

A high Ki67 Labelling Index (missing 121 cases) was found in 14.5% of the 537 evaluated punches and it was significantly associated with a high ChrA expression ( $p < 0.001$ ) (Table-3). The univariate analysis associates ChrA and Ki67 with Gleason score ( $p = 0.002$  and  $p < 0.001$ ) (Table-2). The multivariate analysis (Table-4) further shows all markers but AR in significant test trend association with the Gleason score. Neither ChrA, nor AR and NeuroD1 positive staining were found to be associated with the presence of seminal vesicles, urethral or perineural invasion.

The Kaplan-Meier model curves showed that Gleason score (data not shown) and Ki67 level had a significant influence on survival parameters ( $p < 0.001$ ), whereas ChrA ( $p = 0.7$ ), AR ( $p = 0.8$ )

## Neuroendocrine Differentiation Marker in Human Prostate Cancer

**Table 2** – Pattern of markers expression distributed according to homogeneous pathological group of patients following Gleason score\*.

Pathological Markers	Gleason < 7	Gleason = 7	Gleason > 7	p Value
Neuro D1 (missing N = 249)				0.547
Absent	69 (28.9)	31 (22.6)	7 (21.2)	
Intermediate	77 (32.2)	43 (31.4)	10 (30.3)	
High	93 (38.9)	63 (46.0)	16 (48.5)	
ChrA (missing N = 30)				0.002
Low	216 (59.5)	126 (58.3)	16 (32.7)	
Intermediate	97 (26.7)	51 (23.6)	17 (34.7)	
High	50 (13.8)	39 (18.1)	16 (32.7)	
AR (missing N = 285)				0.142
Low	79 (36.1)	54 (43.5)	9 (30.0)	
Intermediate	78 (35.6)	37 (29.8)	16 (53.3)	
High	62 (28.3)	33 (26.6)	5 (16.7)	
Ki67 (missing N = 121)				<0.001
Low	282 (91.6)	147 (80.3)	30 (65.2)	
High	26 (8.4)	36 (19.7)	16 (34.8)	

\* tables entries are absolute numbers and percentages. ChrA = chromogranin-A; AR = androgen receptor; Ki67 = Ki67 label index.

**Table 3** – Spearman's correlation matrix of marker tissue reactivity\*.

	NeuroD1	ChrA	AR	Ki67
NeuroD1	-	0.187 (<0.001)	0.189 (0.004)	0.013 (0.806)
ChrA	-	-	0.151 (0.004)	0.164 (<0.001)
AR	-	-	-	0.091 (0.115)
Ki67	-	-	-	-

\* tables entries are correlation coefficients and p Values. ChrA = chromogranin-A; AR = androgen receptor; Ki67 = Ki67 label index.

and NeuroD1 ( $p = 0.7$ ) did not show any significant influence on progression-free (Figure-1) and overall survival (data not shown).

### COMMENTS

Although several immunohistochemical studies revealed the presence of NE cells in almost all PCa

(20), their prognostic relevance remain controversial (21). The NED (mainly identified by tissue ChrA positive staining) seems to be useful as predictor for biochemical failure after radical prostatectomy in clinically localized PCa (21-23) and in low Gleason score PCa (23). As far as NE activity is concerned it will be difficult to detect as the knowledge of NED pathophysiology remains obscure, prompting the search for new biomarkers (14). Therefore, we previ-

**Table 4** – Multivariate analysis of association with markers distributed according to homogeneous pathological groups\*.

	NeuroD1	ChrA	AR	Ki67
Age, year	0.99 (0.96-1.01)	0.99 (0.97-1.01)	0.99 (0.97-1.02)	1.00 (0.96-1.03)
Gleason score <sup>^</sup>				
<7 (reference)				
7	1.44 (0.96-2.16)	1.06 (0.75-1.49)	0.77 (0.50-1.17)	2.53 (1.44-4.45)
>7	1.72 (0.82-3.61)	2.88 (1.59-5.22)	0.92 (0.45-1.91)	4.86 (2.21-10.7)
Stage				
pT2 (reference)				
pT3	0.99 (0.57-1.73)	1.02 (0.67-1.56)	1.03 (0.62-1.73)	0.87 (0.43-1.73)
pT4	0.70 (0.28-1.75)	1.14 (0.52-2.54)	0.93 (0.34-2.53)	1.76 (0.67-4.68)
pTx	0.91 (0.47-1.76)	0.71 (0.38-1.32)	0.94 (0.48-1.87)	2.24 (0.95-5.27)
Perineural invasion				
Yes vs No	0.87 (0.59-1.27)	1.23 (0.89-1.69)	1.19 (0.80-1.77)	1.49 (0.89-2.51)

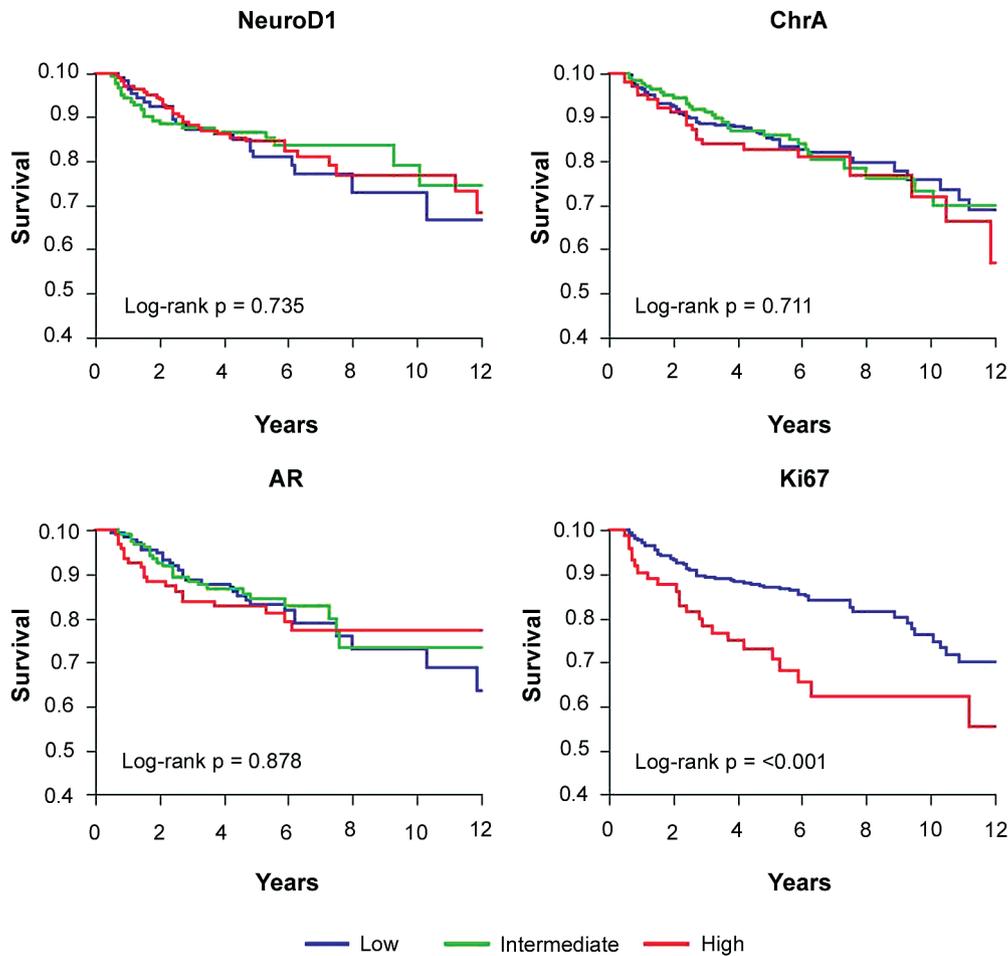
Tables entries are OR and 95% confidence intervals. <sup>^</sup> p for trend test is <0.05 NeuroD1, ChrA and Ki67. ChrA=chromogranin-A; AR=androgen receptor; Ki67=Ki67 label index.

ously investigated the effects of cAMP on epithelial prostate cancer cell lines detecting a significant variation of HOX-D gene expression and identifying the upstream area of the HOX-D locus on chromosome 2q31-33 as potentially involved in a neurogenic program connected to NED (17). Among the genes located in this genomic area, NeuroD1 expression has been related to PCa (14). New evidences have further stressed the use of pro-neural transcription factors, including NeuroD1, as cancer biomarkers (24), suggesting that the aberrant initiation of differentiation programs may confer a selective advantage. The observation that in different PCa models (human derived neoplastic cell-lines, transgenic mouse tumors and patient samples) the hallmarks of neural transdifferentiation along the progression to metastatic disease were associated with changes in the expression of activator-type beta-Helix-Loop-Helix transcription factors including Hes6 and Ascl1 (24) strongly corroborates our findings. The activation of pro-neural transcription factors may well be a crucial step in PCa progression even in a naïve prostate cancer. Through the use of TMA methodology, we have compared different NE markers in patients who underwent radical

prostatectomy for surgically treated naïve PCa. This immunohistochemical assay (IHC) showed a very low expression of NE markers in BPH (data not shown), as previously reported (14). On the other hand, in PCa we found a higher prevalence of NeuroD1 (73% of the cases), Ki-67 (85%) and AR (62%) over ChrA expression (42%), respectively. Herein, we showed that all the markers in our study are mutually and strongly associated (Tables 2 and 3).

The well-documented correlations (18,23,25,26) between the Ki-67 expression and the aggressive features of PCa were confirmed here by the demonstration of its significant association with Gleason score, ChrA expression and survival. On the other hand, the absence of correlation with the NeuroD1 and AR (Figure-2) could be explained by the fact that Ki-67 is only a marker of proliferation, whereas NeuroD1 and AR are implicated into the neuroendocrine differentiation pathway (9,14,27,28).

The evidence of significant associations between ChrA, NeuroD1 and AR probably suggests that their expression is not only correlated, but also that the biological significance remains rather obscure. We can speculate about the functional rela-



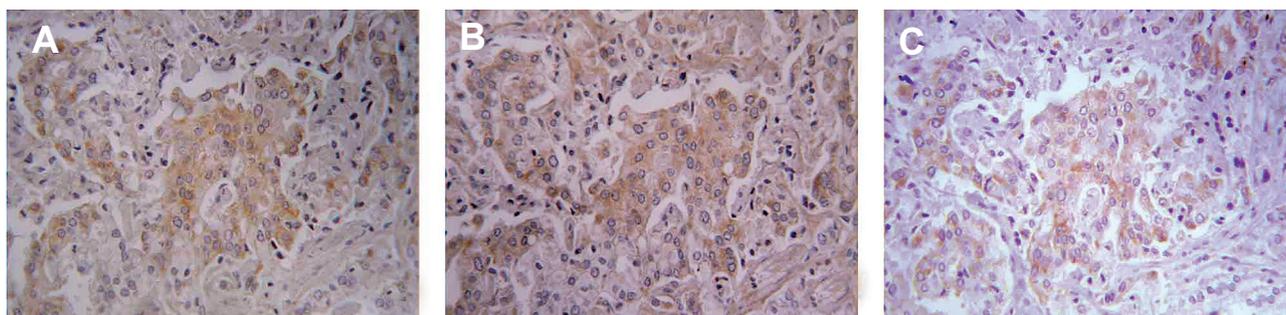
**Figure 1** – Progression free survival according to the markers tissue reactivity. ChrA = chromogranin-A; AR = androgen receptor; Ki67 = Ki67 label index. In the first panel, the blue line is referred to the group without NeuroD1 tissue reactivity indicated as “low”.

tionships in induction or sustain of a neuroendocrine activity or NED in PCa. In the low-grade (Gleason score < 7) group NeuroD1 and ChrA were detected in 71.1 and 40.5% of the cases, respectively. In our opinion this finding is interesting and suggests that NeuroD1 could be activated in prostate tumorigenesis and that it probably is a more accurate marker of transdifferentiated cells or cells predisposed to an early NED.

Further experiments are needed to demonstrate that for the early detection of NE activity an integrated diagnostic panel (e.g. Dopa-Decarboxylase,

a-methylacyl-CoA racemase, IL-8 receptors) should be proposed (9).

A limitation of our study concerns the cut-off values used in the analyses, selected on the bases of the best possible discriminatory effect. This approach may predispose to detect false positive results. However, as Figure-1 indicates, only Ki67 robustly emerged as prognostic variable between the markers tested for prognostic implication. A clear finding of the study is the easy identification of high- and low-progression risk PCa patients, with the majority of patients belonging to the intermediate group by all the markers. The



**Figure 2** – Sequential slides of a same Gleason-4 prostate cancer, showing high chromogranin-A (A) and Neuro D1 (B) positivity with absent expression of androgen receptor (C). Immunohistochemical staining, X40.

intermediate group includes a significant fraction of patients who experience progression of disease, urging for additional markers. Furthermore, we have used an historical (1971-1996) series of surgically treated patients (members of the Kaiser Foundation Health Plan) for the evaluation of the prognostic significance and the internal relationships of the markers. Thus, the likelihood of biases due to patient selection, surgical management, follow-up data and tissue quality is not negligible. On the other hand, the long median follow-up time (almost 6 years with the longest follow-up time being over 12 years) is an interesting argument suggesting that PCa cells may remain dormant for long periods of time (PCa progression can also take place 10 years after prostatectomy). Moreover, data concerning the kind of progression detection (by the use of the preoperative and during the follow-up PSA values or traditional imaging test) are lacking, hindering any possible inference relationship between kind of progression, PSA, NE markers and prognosis.

## CONCLUSIONS

Our study highlights the utility of TMAs to efficiently evaluate candidate prognostic markers in PCa. While some results confirm previous findings, for the first time, to our knowledge, ChrA, AR and NeuroD1 were evaluated together on a prostate TMA. The lack of association between the ChrA, AR and NeuroD1 tissue reactivity and survival suggest that these markers cannot be considered prognostic marker in patients surgically treated for

PCa. Nevertheless, a better identification of such neuroendocrine differentiation could advise about a better response rate after carboplatin-etoposide regimen chemotherapy (29).

Also, the highest reactivity of NeuroD1 over ChrA suggests its possible use, for example, as a target for antisense oligonucleotide therapy (30).

## CONFLICT OF INTEREST

None declared.

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## Learning Curve for Radical Retropubic Prostatectomy

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### ABSTRACT

*Purpose:* The learning curve is a period in which the surgical procedure is performed with difficulty and slowness, leading to a higher risk of complications and reduced effectiveness due the surgeon's inexperience. We sought to analyze the residents' learning curve for open radical prostatectomy (RP) in a training program.

*Materials and Methods:* We conducted a prospective study from June 2006 to January 2008 in the academic environment of the University of São Paulo. Five residents operated on 184 patients during a four-month rotation in the urologic oncology division, mentored by the same physician assistants. We performed sequential analyses according to the number of surgeries, as follows:  $\leq 10$ , 11 to 19, 20 to 28, and  $\geq 29$ .

*Results:* The residents performed an average of 37 RP each. The average PSA was 9.3 ng/mL and clinical stage T1c in 71% of the patients. The pathological stage was pT2 (73%), pT3 (23%), pT4 (4%), and 46% of the patients had a Gleason score 7 or higher. In all surgeries, the average operative time and estimated blood loss was 140 minutes and 488 mL. Overall, 7.2% of patients required blood transfusion, and 23% had positive surgical margins.

*Conclusion:* During the initial RP learning curve, we found a significant reduction in the operative time; blood transfusion during the procedures and positive surgical margin rate were stable in our series.

*Key words:* prostatic neoplasms; prostatectomy; learning; internship and residency; postoperative complications  
*Int Braz J Urol. 2011; 37: 67-78*

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### INTRODUCTION

Prostate cancer (PCa) is currently the most common malignant tumor among men in Europe and the United States (US), except for malignant non-melanoma skin tumors. In the US, it is estimated that about 192,280 new cases are diagnosed per year, with 27,360 deaths a year due to PCa, which represents 9% of all cancer deaths in the country per year (1). In Europe, each year there are an estimated 190,000 new cases, with more than 50,000 deaths from the disease (2).

Radical prostatectomy (RP) was the first widely used standard treatment for localized PCa. The classic approach is the retropubic technique. RP was

introduced in 1905 by Young and reviewed by Millin in 1946. However, it only became routinely and safely performed in 1982, when Walsh et al. published new technical aspects of the surgery, definitely setting the surgical standards for the treatment of PCa (3). Since then, new techniques and approaches have been developed, such as perineal (4), laparoscopic (5,6) and robotic-assisted RP (7). Throughout the first decade of the 21st century, the use of robotic-assisted surgery has rapidly increased in the U.S. (1), spanning the last three years to Europe (2) and finally to Brazil in 2008 (8).

Subsequently new technological elements have been incorporated into the surgical technique of RP, and increasingly high additional direct and

indirect expenses have significantly added to the total cost of the procedure. Notwithstanding the problem of significantly elevated costs, technological complexity incorporated into new techniques may result in a longer or yet unclear learning curve (9).

High costs and a possibly longer learning curve prompted us to question the applicability of these new surgical modalities into clinical practice of our hospitals, especially those related to the public health system of our country. Furthermore, there still lacks a thorough discussion of their unclear benefits to oncologic outcomes and quality of life of patients who undergo minimally invasive procedures (10). To what extent have perineal, laparoscopic or robotic-assisted RP proved superior to the open retropubic approach?

The learning curve in surgery can be defined as the number of cases required to perform the procedure with reasonable operating time and an acceptable rate of complications, resulting in an adequate postoperative clinical outcome associated with a shorter hospital stay. Obviously, several key factors may impact the learning curve, not only such as those related to the surgeon, as attitude, confidence, experience with other surgical procedures, but also those related to the team members involved in the procedures. Undoubtedly, the number of cases performed by the surgeon and the volume of surgeries in a given center may certainly delineate the course of surgical outcomes (11).

RP is a particularly complex surgical procedure and it is assumed to be closely related to the surgical technique employed, depending in part on the surgeon's experience. Currently each RP technique, either open (retropubic and perineal), or minimally invasive (laparoscopic and robotic), present distinctive learning curves for the surgeon.

Due to the wide variation in training formats offered in the various surgical programs in urology, we sought to evaluate the learning curve for open RP among third-year urology residents (fifth year of residency in surgery overall) in a high volume tertiary referral center. We aimed at both defining a minimum number of procedures necessary to properly train the resident surgeon in urology for this procedure, as well as on determining the most sensitive key points of the learning

process. As a result, we may be able to continuously improve the teaching process of the surgical technique and make it widely available to mentors and teaching centers, especially considering the social environment of growing ethical concerns with patient safety.

## MATERIALS AND METHODS

We conducted a prospective study from June 2006 to January 2008 in the urologic oncology division of the University of São Paulo. Patients with clinically localized prostate adenocarcinoma (cT1-2 Nx M0) with medical conditions for surgical treatment were selected. Five residents operated on 184 patients during a four-month rotation in the urologic oncology division, mentored by the same physician assistants. Patients who had undergone other treatments such as chemotherapy, radiation therapy or biological agents prior or concomitant to surgery and patients with significant neurological, psychiatric disorders, including dementia or seizures, were excluded from the study.

Surgeries were performed following the same surgical technique for radical retropubic prostatectomy, as previously described (11,12). In all surgeries, the residents were assisted by 5 attending surgeons. Fifteen days after hospital discharge, the indwelling catheter and stitches were removed. The first functional evaluation (urinary incontinence) was 60 days after surgery, as well as laboratory tests (PSA value, blood count and serum creatinine).

The length of operative time was measured from skin incision until the completion of the wound dressing. The estimated blood loss was calculated by measuring the volume of the vacuum bottle minus the amount of saline used during surgery. No sponges were used during surgery.

We also assessed the surgical pathology stage and Gleason score, in all cases, as well as positive surgical margin for extracapsular extension. Statistical analysis was performed by using analysis of variance (ANOVA) and the number of surgeries in quartiles: up to 10, from 11 to 19, from 20 to 28 and more than 29 surgeries. Fisher's exact test was applied to evaluate the groups.

## Learning Curve for RRP

**Table 1 – Distribution of the number of surgeries performed in accordance with month of training and residents.**

	1st Month	2nd Month	3rd Month	4th Month	Total
Resident #1	7	3	12	6	28
Resident #2	12	8	11	10	41
Resident #3	17	9	11	1	38
Resident #4	11	4	6	22	43
Resident #5	12	9	4	9	34
Total	59	33	44	48	184

## RESULTS

Each resident participated in the study during four consecutive months and, on average, each one of them performed 9 surgeries per month (Table-1).

The demographics of patients who underwent RP are summarized in Table-2.

The surgical pathology stage, prostate size, Gleason score and surgical margins are summarized in Table-3.

Table-4 presents surgical data. The median operative time was 140 minutes, and most patients did not require blood transfusion.

A curve of decreasing operative time ( $p = 0.03$ ) is shown in Figure-1, comparing the 19 initial RP to the following 9 RP performed ( $p = 0.01$ ) and the remaining surgeries from 29 and more ( $p < 0.001$ ). From the twentieth RP onwards, we found a significant decrease in the operative time.

There was a progressive decrease in estimated blood loss as the residents gained surgical experience with RP, as shown in Figure-2.

**Table 2 – Clinical characteristics of all patients.**

Age (years)	
Median (Q1 – Q3)	64 (58 – 70)
Range	42 – 79
PSA (ng/ml)	n = 181
Median (Q1 – Q3)	7.3 (4.7 – 11.5)
Range	0.6 – 44.0
Prostate weight	n = 182
Median (Q1 – Q3)	30 (30 – 40)
Range	20 – 100
Clinical Stage	
T <sub>1</sub>	132 (71.7%)
T <sub>2</sub>	52 (28.3%)
Gleason Score	
< 7	123 (66.8%)
7	42 (22.8%)
> 7	19 (10.4%)

**Table 3 – Surgical pathology features at radical prostatectomy.**

TNM	N = 184 (%)
pT <sub>0</sub> , N <sub>x</sub> , N <sub>0</sub>	4 (2.2)
pT <sub>1</sub> , N <sub>x</sub> , N <sub>0</sub>	4 (2.2)
pT <sub>2</sub> , N <sub>x</sub> , N <sub>0</sub> , N <sub>1</sub>	133 (72.6)
pT <sub>3</sub> , N <sub>x</sub> , N <sub>0</sub> , N <sub>1</sub>	42 (23.0)
Gleason score	
< 7	102 (55.4)
7	79 (32.1)
> 7	19 (10.3)
Positive surgical margin*	
Apical	28 (15.2)
Vesical	13 (7.1)
Lateral/Posterior	12 (6.5)
Prostate weight	
≤ 40g	101 (56.1)
41 – 80g	63 (35.0)
> 80g	16 (8.9)

\* positive margins may be concomitant. TNM = tumor node metastasis staging.

Learning Curve for RRP

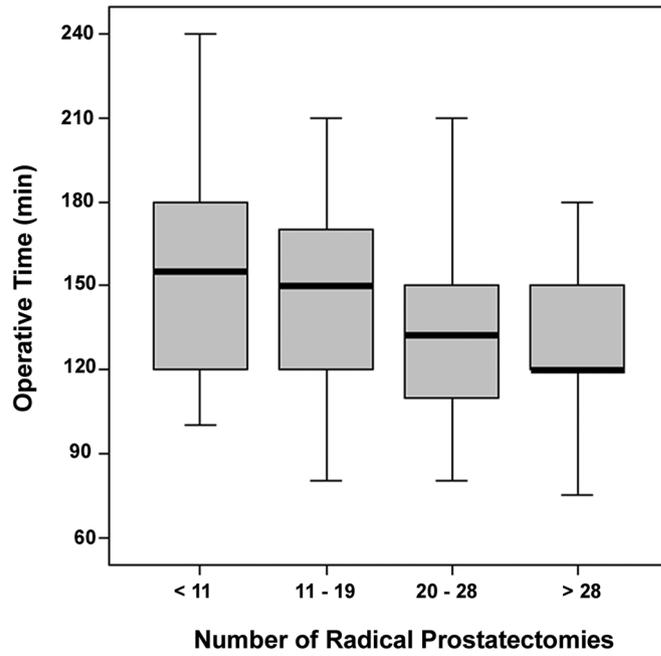


Figure 1 – Box-plot of operative surgical time according to the number of surgeries.

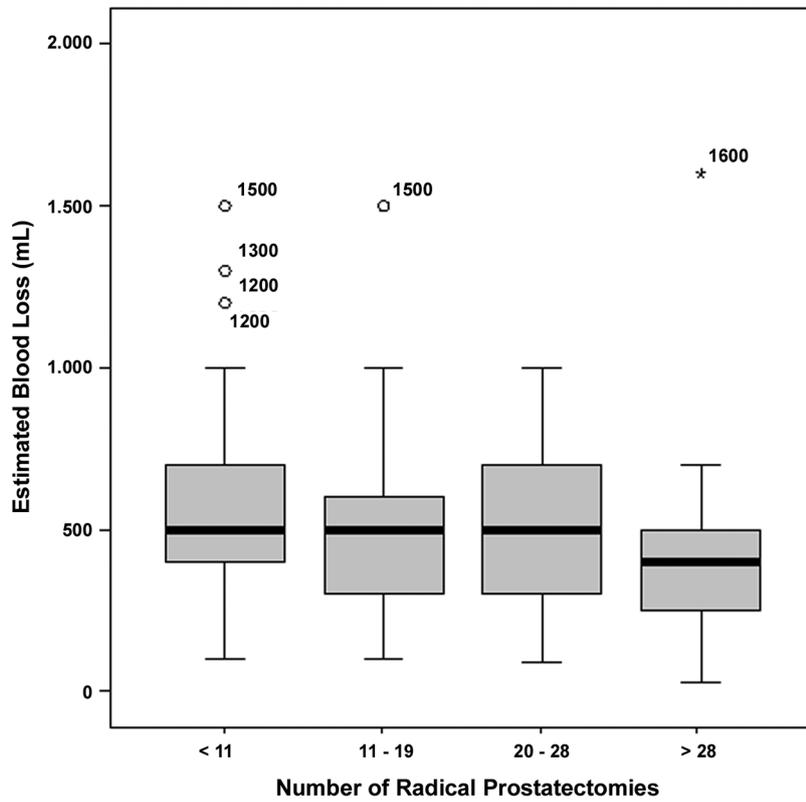


Figure 2 – Box-plot of estimated blood loss according to the number of surgeries.

**Table 4 – Intraoperative data.**

Estimated blood loss	
Median (Q1 – Q3)	488 (300 – 600)
Range	90 – 1600
Blood transfusion	
No	168 (92.8%)
Yes	13 (7.2%)
Operative time (min)	
Median (Q1 – Q3)	140 (120 – 160)
Range	75 – 240

Figure-3 shows the association between the number of surgeries performed and need for blood transfusion, where a 3% transfusion rate was observed after the 29th surgery.

When the resident operated on smaller prostates, blood transfusion was rarely required, as highlighted in Tables 5 and 6, where prostates < 40g and > 40g required a blood transfusion in 3% and 13% of RP, respectively.

In reviewing the occurrence of positive surgical margins, we observed that it remained stable during the four phases, as shown in Table-7.

**COMMENTS**

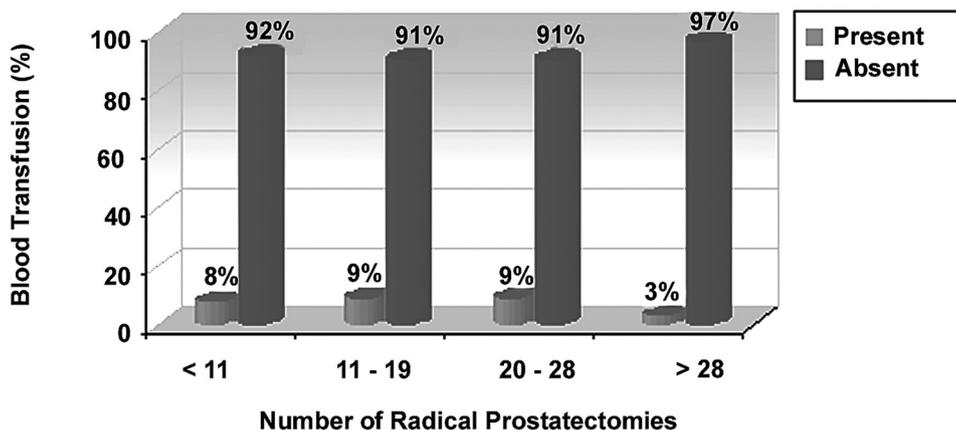
The RP learning curve for residents showed that after twenty surgeries, there was a signifi-

cant reduction in operative time from 150 to 120 minutes and, after the 29th surgery, the need for blood transfusion also decreased from 9% to 3%. Moreover, the percentage of compromised surgical margins remained stable during the learning curve.

The discussion regarding the learning curve in RP has not been frequently addressed in clinical studies and few series have reported clinical and pathologic data exclusively of residents in training instead of only experienced surgeons (13,14). Published evidence has demonstrated that the number of RP previously performed by the surgeon affects patient outcomes. It is believed that a learning curve of 200 cases would be necessary to achieve an “expert” status (13,15).

A recent prospective study evaluated surgeons after a urologic oncology fellowship program, after they had already completed an initial learning curve of an average of 47 cases during residency and another 87 RP performed during the fellowship (15). The mean operative time was 201 minutes, the estimated blood loss was 734 mL, with a 6% rate of blood transfusion.

The learning curve is a major problem in surgery, during which the surgical procedure is usually performed with more difficulty and slowness, associated with a higher risk of complications and low efficacy due to inexperience of the surgeon. If an initial assessment is made, the learning curve is primarily a theoretical concept, because this is a theme or line



**Figure 3 – Distribution of the number of blood transfusions according to the number of surgeries.**

**Table 5** – Blood transfusion in radical prostatectomies of prostates  $\leq 40g$ .

Number of Surgeries	Blood Transfusion		
	Absent (%)	Present (%)	Total (%)
10 and under	26 (96.3)	1 (3.7)	27 (100)
11 - 19	23 (95.8)	1 (4.2)	24 (100)
20 - 28	22 (95.7)	1 (4.3)	23 (100)
29 or more	26 (100.0)	0	26 (100)
Total	97 (97.0)	3 (3.0)	100 (100)

Fisher's exact test:  $p = 0.796$ .

**Table 6** – Blood transfusion in radical prostatectomies of prostates  $> 40g$ .

Number of Surgeries	Blood Transfusion		
	Absent (%)	Present (%)	Total (%)
10 and under	20 (87.0)	3 (13.0)	23 (100)
11 - 19	17 (85.0)	3 (15.0)	20 (100)
20 - 28	18 (85.7)	3 (14.3)	21 (100)
29 or more	13 (92.9)	1 (7.1)	14 (100)
Total	68 (87.2)	10 (12.8)	78 (100)

Fisher's exact test:  $p = 0.937$ .

of research rarely present in residency programs and urologic literature.

The surgeons gain much of the knowledge necessary for surgical procedures during medical residency programs. In the learning process, the urology resident trains in the areas of endourology, incontinence and reconstruction, erectile dysfunction and infertility, pediatric urology and kidney transplantation, laparoscopy and cryotherapy. Within the urologic oncology division, several surgeries are performed, such as transurethral resection of the prostate and bladder, cystectomy and urinary reconstruction, retroperitoneal lymphadenectomy and open and laparoscopic nephrectomy, fostering a growing field of surgical procedures and greater confidence to perform them. The American Urological Association reported that the number of RP

performed by residents has declined in recent years, and overall 84% of surgeons have performed less than ten RP annually (8). Based on these data, we can infer that much of the surgical experience needed to acquire proficiency in complex procedures can only be acquired during residency. Eventually, according to local community demand or the volume of surgeries performed at the hospital, this development may never occur.

The percentage of compromised surgical margins varies with the surgeon's experience in this procedure. According to a landmark study by Vickers et al., the rate of positive margins was 36% before 50 RP performed, 29% with 50 to 99 RP, 23% with 100 to 249 RP, 22% with 250 to 999 RP, and 11% with 1000 RP or more (16). Overall, the surgical margin status was positive in 22.9% of surgeries.

**Table 7** – Positive surgical margins during learning curve.

Number of Surgeries	Extracapsular Margin		
	Negative (%)	Positive (%)	Total (%)
10 or under	40 (80.0)	10 (20.0)	50 (100)
11 - 19	35 (77.8)	10 (22.2)	45 (100)
20 - 28	35 (76.1)	11 (23.9)	46 (100)
29 or more	32 (74.4)	11 (25.6)	43 (100)
Total	142 (77.2)	42 (22.8)	184 (100)

$p = 0.929$ .

Regarding minimally invasive RP techniques, usually performed by surgeons in large centers with extensive surgical experience, data on robotic and laparoscopic was as follows, respectively: blood transfusion 3% and 9.8%, positive surgical margin of 15.8% and 19.5%, mean operative time was 166 and 160 minutes, and average hospital stay of 5.4 and 4.9 days (17). A study describing the learning curve of robotic RP showed that the robotic surgeon with up to 12 surgeries had an average operative time of  $242 \pm 64$  minutes and 58% of cases with positive margins; with 13 to 188 robotic RP, the operative time was reduced to  $165 \pm 45$  minutes and positive margins to 23%. Surgeons who performed more than 189 robotic RP had an average operative time of  $134 \pm 45$  minutes and positive margins in 9% (18).

The following strengths can be highlighted in the present study: a homogeneous group of residents in training who had never performed a RP was included; the prospective design of the study allowed us to perform the same surgical technique and mentored by the same group of physician assistants; and the sample size accrued was reasonable. Therefore, we believe that these results may generate important information on surgical training and education in urologic oncology.

The fact that the surgeon is inexperienced, starting the learning curve with this procedure, may be of benefit by rapidly improving the performance in the short term, considering that a homogenous and standardized teaching methodology is applied. As our data suggests, it renders the possibility to generate

less intraoperative morbidity and lower rate of positive surgical margins, improving the clinical course of patients.

## CONCLUSIONS

Open radical prostatectomy is a safe and effective procedure that can be done on a large scale in teaching institutions, as long as a structured training program provides adequate teaching methods. During the initial training experience of a surgeon, a steep reduction in blood transfusions and a quick stabilization of the learning curve after twenty procedures can be expected.

## CONFLICT OF INTEREST

None declared.

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## EDITORIAL COMMENT

Open radical prostatectomy is the gold standard and most widespread treatment for clinically localized prostate cancer.

About thirty years ago the first purposeful nerve sparing radical prostatectomies were performed by Dr. Patrick Walsh. Since then, a better understanding of the periprostatic anatomical results with continued improvement in functional outcomes and oncological control for patients undergoing radical prostatectomy, whether by open or minimally-invasive surgery.

The oncologic results of author's paper in an important center of high volume treatment of prostate cancer are in line with those reported with the use of the retropubic approach. With a "homogenous and standardized teaching methodology", the residents can achieve good data as regards less intraoperative morbidity and lower rate of positive surgical margins, improving the clinical course of patients.

The learning curve in surgery can be defined as the number of cases required to perform the procedure with reasonable operating time and an acceptable rate of complications, resulting in an adequate post-operative clinical outcome associated with a shorter hospital stay (1).

A paper was published about the learning curve for surgery for prostate cancer recurrence after radical prostatectomy. The study cohort included 7765 prostate cancer patients who were treated with radical prostatectomy by one of 72 surgeons at four major US academic medical centers between 1987 and 2003. The learning curve for prostate cancer recurrence after radical prostatectomy was steep and did not start to

plateau until a surgeon had completed approximately 250 prior operations (2). As a surgeon's experience increases, cancer control after radical prostatectomy improves.

These results may generate important information on surgical training, improve the teaching process of the surgical technique and make it widely available to mentors and teaching centers, especially considering the social environment of growing ethical concerns with patient safety. Further research is needed to examine the specific techniques used by experienced surgeons that are associated with improved outcomes.

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## EDITORIAL COMMENT

The learning curve plateau comes with training and experience. Surgeons have always recognized a structured way to introduce new procedures: learning a new technique requires dedication.

If we try to define a learning curve, we should look back at the work of Dr. Donald Ross - a pioneer in cardiac surgery in the United Kingdom - who proposed the Ross procedure in 1962 (1). The Ross

procedure, first performed in 1967, is a challenging operation for patients with aortic valve disease. The principle is to remove the patient's normal pulmonary valve and used it to replace the patient's diseased aortic valve. In Dr. Ross's own series, 23% of the patients died during the first year of the operation and 18% in the second year. The following 10 years, surgical mortality in a series of 188 patients dropped to 9%. This is a learning curve. The message: it requires time and hard work.

How many cases do we need to become expert surgeons in the technique we perform on an everyday basis? The latter remain a controversial question for the field of radical prostatectomy. The arrival of both, laparoscopy and later robotic surgery has put on stage the term learning curve. In fact, laparoscopic series brought with them a tremendous enthusiasm in terms of validation of the technique and therefore extensive work in the procedure's learning curve.

In our experience at the Institut Montsouris in Paris, it was hard to keep in mind Dr. Walsh's concepts on radical prostatectomy and simultaneously comply with the demanding endoscopic surgical environment, but a step-by-step structured training brought us through the task.

The paper on the learning curve of retropubic radical prostatectomy presented by Dall'Oglio et al. in this issue of *IBJU*, represents a comprehensive analysis of the initial experience of a group of residents with retropubic prostatectomy, perhaps missing in the literature. The paper offers real information gained by surgical experience and presents a sincere vision of a proctored prostatic surgical approach in the everyday world.

Dall'Oglio et al. found in their interesting analysis, that improvement of clinical outcomes can be seen after 20 to 30 cases. We could say that these findings are far from those presented by Vickers et al in their timely publication assessing surgical learning curve for prostate cancer control (2). Vickers et al. found statistical significance related to surgeon's experience and cancer control after radical prostatectomy in an analysis of highly dedicated surgeons. This study brought back to reality the definition of learning curve in radical prostatectomy, reflecting a real link between surgi-

cal technique and cancer control, and establishing the concept of a dramatic improvement in cancer control with increasing surgeon experience up to 250 previous treated cases. That said, we must agree with Dr. Stuart Howards in the fact that it is somewhat arbitrary to assert that it is necessary to perform 250 procedures to become competent and provide good cancer control (3). Therefore, establishing solid bases for radical prostatectomy performed in a Urology program, is an important challenge to any institution and it requires hard dedication and a focused operating room team; but as presented in the Dall'Oglio et al. study this is a feasible task and it might get the future urologists ready to finish their training and be able to offer a surgical procedure of the highest quality.

The future seems difficult for the young urologist, because as presented by Ficarra et al., positive surgical margin rates decreased with the surgeon's experience and technique improvement, reaching similar percentages for retropubic, laparoscopic and robotic series (4); but perhaps the positive surgical margins are not so secure as oncological endpoint (5) and even our current definitions for biochemical recurrences do not substantially impact prognostic factor estimates. This situation implies that the training period should provide solid concepts to build a professional career, and because knowledge and concepts might and will change; an academic way to learn, and eventually teach, is the way that it ought to be in order to assure the adequate surgical treatment of patients, in years to come.

With a structured methodical system, it is possible to implement radical prostatectomy safely and effectively without compromising morbidity, oncological and functional outcomes. A team-based approach helps to reduce the learning curve of the procedure for individual surgeons. This was our initial approach for laparoscopic and robotic prostatectomy at our institution.

The fruit you harvest from the three in this interesting publication is that we must be sure to teach the philosophy of how to adequately treat localized prostate cancer and then, we must get in the operating room with the urologists-in-training to provide them with the basic tools that will hopefully sustain future reliable operators.

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## REPLY BY THE AUTHORS

Both editorial comments reassured the importance of a structured learning methodology in the surgical field and pointed out the feasibility of safely teaching complex procedures, such as radical prostatectomy. In our study, we sought to demonstrate a real learning curve of inexperienced surgeons, on which we could evaluate both an increasing growth in surgical skills from an early starting point, combined with the radical prostatectomy training itself. This was possible due to a homogeneous group of mentors, all of them with more than 200 prostatectomies performed.

As mentioned in the editorial, the landmark paper by Dr. Vickers demonstrated a long learning curve, on which improvements were observed to 250 cases performed (1). This study differed significantly from ours, since not only no standardized surgical methodology was applied by all 72 surgeons, but also several very experienced surgeons after urology training were included in the study.

Although our learning curve demonstrated an initial experience with radical prostatectomy,

the standardized technique had been extensively improved and validated by Prof. Miguel Srougi, throughout his 4,000 cases (2,3). Currently, two participating residents in the study are now mentors of the residents at our institution.

A further study is now being finalized and will focus on the initial 100 consecutive cases operated with this same standardized technique, with a larger number of surgeons, due to the expansion of our program. Therefore, we expect to generate a stronger evidence to support the use of our teaching methodology, which may help to create a gold standard approach for urology training programs throughout the country.

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# Reducing Infectious Complications after Transrectal Prostate Needle Biopsy Using a Disposable Needle Guide: Is It Possible?

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## ABSTRACT

*Purpose:* To investigate whether the use of a disposable needle guide results in a decreased incidence of infectious complication after transrectal prostate needle biopsy (TPNB).

*Materials and Methods:* Fifty five patients who underwent 10-core TPNB were randomized into two groups. A pre-biopsy blood and urine examination was performed in both groups. Group 1 (25 patients) underwent biopsy with disposable biopsy needle guide and Group 2 (30 patients) underwent biopsy with reusable biopsy needle guide. All patients had a blood and negative urine culture before the procedure. The patients received ciprofloxacin 500 mg twice a day beginning the day before the biopsy and continued for 3 days after. Serum C-reactive protein levels and urine and blood specimens were obtained 48h after the biopsy. Primary endpoint of the study was to determine the effect of needle guide on the bacteriologic urinary tract infection (UTI) rate and secondary end point was to determine symptomatic UTI.

*Results:* The mean age of the patients was 63.46 (range 55 to 68) years. There were no significant differences regarding the prostate-specific antigen level, prostate size, existence of comorbidity in two groups before the procedure. Bacteriologic and symptomatic UTI was detected in 4% vs. 6.6% and 4% vs. 3.9% in Group 1 and 2 relatively ( $P > 0.05$ ).

*Conclusion:* The use of a disposable needle guide does not appear to minimize infection risk after TPNB. Large scale and randomized studies are necessary to determine the effect of disposable needle guide on infection rate after TPNB.

*Key words:* prostate; biopsy; needle; infection

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## INTRODUCTION

Transrectal ultrasound (TRUS) guided needle biopsy of the prostate is the most common modality used to diagnose prostate cancer. Since male individuals in a screening population are asymptomatic, biopsy procedure should be safe and morbidity should be kept to a minimum. Transrectal prostate needle biopsy (TPNB) is safe for diagnosing prostate cancer with few major, but frequent minor complications, such as hematuria and hematospermia (1,2). Infectious

complications after TPNB are an important issue of concern. Currently, many urologists use prophylactic antibiotic therapy and/or enemas to minimize infection-related complications; however, such therapy does not completely eliminate the risk of infection (3). The infectious complications associated with this procedure include: asymptomatic bacteriuria, fever, symptomatic urinary tract infections (UTIs), and bacteremia (4,5).

Although many biopsy protocols have been described to reduce infectious complications after a

TPNB, such as modified bowel preparation, different type and duration of antibiotic prophylactic schemes, and number of biopsy cores (6,7). The role of a disposable needle guide to reduce the infection rate has not been adequately assessed. The notion that biopsy equipment, such as reusable guides, may be important as a contamination site for bacteremia, was first evaluated by Tuncel et al. (8). A disposable TRUS-probe needle guide (Matek; Geotek, Inc., Ankara, Turkey) has been developed to reduce the possible source of infectious complications and has been on the market in Turkey for 3 years.

We prospectively investigated whether the novel disposable TRUS-probe needle guide may decrease infectious complications after TPNB.

## MATERIAL AND METHODS

Between January and June 2009, 55 patients were included in this study. All participants gave written informed consent. The local ethics committee approved the study. The mean age of the patients was 63.46 years (range 58-66 years) in the present study. The patients in whom TRUS-prostate biopsy was planned because of elevated prostate-specific antigen (PSA) levels were included in the study. Exclusion criteria included the following: patients who had an indwelling Foley catheter, symptomatic or asymptomatic UTIs, bleeding disorders, acute prostatitis before prostate biopsy, a previous prostatic biopsy or prostatic surgery, or any antibiotic treatment or anticoagulant therapy.

A midstream urine culture, serum C-reactive protein (CRP) level, and WBC count of all patients were obtained two days before the procedure. The biopsy procedure was performed with the patients in the left lateral decubitus position using a Toshiba Fabio scanner with a 7.5 MHz bi-planar probe attached (Toshiba, Tokyo, Japan).

Patients were randomized into 2 groups by using sealed, opaque envelopes; in Group 1 (25 patients) the biopsy was performed with disposable TRUS-probe needle guide; and in Group 2 (30 patients) the biopsies were performed with a reusable needle guide. A completely disposable apparatus of single unit construction designed for operative use

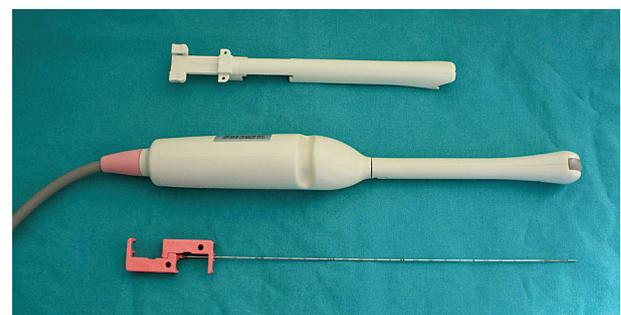
in conjunction with a transrectal ultrasound probe when performing TPNB are presented in Figure-1. The separable and detachable features of the reusable needle guide are presented in Figure-2.

Peri-operative prophylaxis included administration of 500 mg of ciprofloxacin orally the night before the procedure, and an enema per rectum 1 hour before the procedure. Patients were instructed to continue to take ciprofloxacin 500 mg p.o. bid 3 days after the procedure.

Before the biopsy, a standard condom was fitted over the distal tip of the TRUS-probe and filled with lubricant gel. Depending upon randomization, either a reusable or a disposable needle guide was then fitted over the probe and the first condom. A second condom was fitted over these items and filled with lubricant gel. All patients received local anesthesia, consisting of 10 mL 1% lidocaine. Injection was performed around the neurovascular bundle at the prostatic base and apical location with an 18 gauge 20 cm needle by inserting the needle through the needle guide under TRUS guidance and entering Denonvilliers' fascia. Infiltration was done on each side of the



**Figure 1** – Disposable Needle Guide (Matek; Geotek, Inc., Ankara, Turkey) disposable needle guide.



**Figure 2** – Reusable needle guide and transrectal probe.

prostate for a total of 2 punctures. The 10 core prostate biopsies were taken with a spring-loaded biopsy gun (C.R. Bard, Inc., Covington, GA, USA) and an 18 gauge Tru-cut biopsy needle. The core sampling notch was approximately 17 mm long by 1.2 mm in diameter. Repeated biopsy specimen collections were performed using the same needle. The procedure including ultrasound examination and biopsy required 10 minutes on average.

Upon completion of the procedure, the ultrasound probe was disinfected by wiping it with a 3.2% glutaraldehyde solution. The reusable needle guide has two separate pieces which form a lumen after being attached together. The reusable needle guide was soaked in a glutaraldehyde solution for at least 30 minutes, then rinsed with sterile saline and wiped off.

UTI was defined as bacteriologic UTI (bUTI): A patient with a blood or urine culture positive for a known uropathogen and symptomatic UTI (sUTI): A patient with an acute onset of one or more symptoms of dysuria, hematuria, frequency, urgency, urinary retention, suprapubic pain, flank pain, or rigors that have positive urine culture (a growth of  $\geq 10^5$  colony forming units per mL).

A midstream urine culture and blood cultures were obtained from each patient on day 2 after the biopsy and repeated on day 14 after the biopsy. Patients recorded oral body temperature twice daily for 2 weeks. Patients were asked to return for a follow-up visit 14 days after the biopsy. They were also advised to return immediately if they had any complication, such as a high fever, chills.

Primary end-point of the study was to determine the effect of needle guide on the bUTI rate. Secondary end point was sUTI. Clinical symptoms and signs of infection were monitored weekly by office interview.

Complications necessitating hospitalization during the 2 week post-biopsy period were defined as serious. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows Version 13.0 software (SPSS, Inc, Chicago, IL, USA). Mean ages, serum total PSA levels, total prostate volume, comorbidities, CRP and WBC in the groups were compared using univariate analysis of variance test. Chi-squared test was used to compare

infectious complication rates between the groups. A p value less than 0.05 was considered significant with a 95% confidence interval.

## RESULTS

There were no significant differences between the two groups before the TPNB with respect to PSA levels, co-morbidities, CRP levels, and WBC counts. The data for each group is summarized in Table-1. The infectious complications are presented in Table-2. Bacteriologic UTI was observed in 3 patients (1 in Group 1 and 2 in Group 2). A total of 2 patients had Escherichia Coli (E. Coli) in blood culture (1 in each Group) and CRP levels were four times higher than before the TPNB in both groups. Two patients (1 in each Group) with high fever were admitted to the hospital and received intravenous antibiotic therapy. After receiving intravenous antibiotic therapy, the high fever and elevated CRP levels were controlled within 48 hours. E. Coli was harvested in urine culture in 1 patient in Group 2. This patient required hospitalization due to extended-spectrum beta-lactamase (ESBL) producing E. Coli harvested in urine culture in Group 2. No elevated CRP level or any signs of infection were recorded in this patient. Symptomatic UTI was diagnosed in 2 patients (1 patient in each group) caused by E. coli and received oral antibiotic therapy. All isolates were ciprofloxacin resistant. Bacteriologic and symptomatic UTI was detected in 4% vs. 6.6% and 4% vs. 3.9% in Group 1 and 2 respectively ( $p > 0.05$ ).

## COMMENTS

The use of needle guide for TPNB reduces technique variability; leading to a shorter learning curve for biopsy procedure; reduction in procedure time; and a consistent replicable procedure (9). However, the risk of cross-contamination is questionable. The disposable needle guide was introduced into the market in an effort to reduce the risk of infection.

The clinical infection rates after TRNP vary between 0.25 and 5% in past series, though other authors have reported rates of up to 7.5% (10,11).

After biopsy incidence of bacteremia and bacteriuria were reported as 15% to 73% and 30% to 53% respectively (12,13). Lindert et al. reported that bacteremia and bacteriuria after TPNB are common but usually asymptomatic (4). Urine cultures alone may not be useful for diagnosing infection (14). There is no unifying definition of infectious complications after TPNB. However, bacteriologic investigation (bacteriuria [more than  $10^5$  CFU/mL] versus no bacteriuria and bacteremia) and clinical diagnosis (no clinical symptoms of UTI versus clinical signs of UTI) at follow-up are determinant factors to evaluate the complications after TPNB. The clinical importance of positive urine culture in asymptomatic patients is unclear but one asymptomatic patient in group 2 required hospitalization due to ESBL producing *E. Coli* harvested in urine culture.

Bacteriologic UTI rate was found to be statistically similar in both groups. (4% vs. 6.6%).

Hospitalization was required in 4%, 6.6% in Group 1 and Group 2 relatively. The failures of quinolone prophylaxis might be the reason. Worldwide, quinolone-resistance rates among gram-negative bacilli are rising rapidly. Turkish Urinary Tract Infection Study Group recommended that fluoroquinolone-sparing agents should be evaluated as alternative therapies by further clinical efficacy and safety studies (15). Ozden et al. reported the high incidence of ESBL producing *E Coli* after TRNP (16). New preventive protocols might be necessary for TPNB.

Obek et al. reported periprostatic lidocaine infiltration may be associated with a higher risk for infection due to the extra 2 punctures of lidocaine injection into the periprostatic area through the rectum, which is known to be highly colonized by bacteria (17). Intracapsular punctures during anesthesia can also contribute to the increased rate of infection after biopsy but both groups received the same type of periprostatic anesthesia in this study.

There are many factors that are related to the risk of infectious complications in prostate biopsies, such as lack of standardization among urologists in pre-biopsy antimicrobial prophylaxis, high incidence of resistant organisms, and the different methods of disinfection for reusable guides. Contamination of the tools used in biopsies has been reported to be the possible cause of infections occurring after TRUS-guided

prostate biopsies (18). These devices have a needle guide that directs biopsy needle insertion. The biopsy needle repeatedly traverses the guide, affording the opportunity for fecal and blood materials to accumulate. Bioburdens can also accumulate in other parts of the transducer assembly. Brushes are required to clean the transducer assemblies to reduce the bioburden and remove proteins. Transducer assembly kits have not always been supplied with brushes. Not using brushes for cleaning has resulted in improperly reprocessed transducer assemblies, which could lead to pathogen transmission between patients. Gillespie et al. (5) detected an outbreak of *Pseudomonas aeruginosa* after prostate biopsy due to the insufficient manual cleaning of reusable needle guides. They concluded that clinicians performing TRUS-guided prostate biopsy procedures should follow the manufacturer's needle guide reprocessing recommendations or use disposable needle guides. In this study we used the Toshiba Fabio reusable needle guide. According to our results, all types of infectious complications such as asymptomatic bacteriuria, acute urinary infection, high fever, and bacteremia occurred at a statistically similar rate in both groups.

The permanent reusable needle guide, which has a long, narrow lumen may not have allowed adequate sterilization, as mentioned in previous studies, and may be the basis for the increased risk of infectious complications. It is essential to review the manufacturer's reprocessing recommendations and to establish appropriate procedures to avoid potential transmission of pathogens and subsequent patient concerns.

Potential sterilization problems with prostate biopsy equipment encourage the use of disposable equipment. Tuncel et al. (8) first reported that the use of a disposable needle guide reduces infectious complications. These authors determined that asymptomatic bacteriuria, high fever, and acute UTIs were statistically lower in the disposable group compared to the reusable group (4.5% vs. 9%; 5% vs. 10%; and 2% vs. 9%, respectively). Inadequate flushing of the lumen with disinfectant to eradicate microorganisms and the lack of availability of a device to clean the long, narrow lumen was suggested as the major problem with the use of a reusable needle guide for infectious complications. They concluded that the

novel device which has been used as a disposable needle guide is a good alternative to reduce infectious complications. Our results are inconsistent with the results of the initial study but our study population was smaller than previous study populations, possibly affecting the power of our study. However, if the infectious complications occur due to the contamination of the needle guide, it may also occur due to the multiple reintroduction of the needle during the same biopsy. Using a reusable needle guide, even if the needle guide is changed after each pass of the needle, would provide little difference versus a disposable guide. The other explanation is that the physical features of the reusable needle guide in this study may have allowed proper sterilization. The separable and detachable features of the needle guide may be an important factor to prevent the possible infections. The permanent type of reusable needle guide which has been used in Tuncel et al. study (personal info from the author) might not have allowed the appropriate cleaning.

The core sampling notch was approximately 17 mm long by 1.2 mm in diameter. The procedure time including anesthesia application was 15 minutes for each case. There were no major technical problems during the procedure. However, the core length and the procedure time or some minor technical problems may individually affect the infection rate. We did not focus on this issue.

In our study, there were no statistically significant differences between the two groups regarding co-morbidity. Therefore, it is difficult to conclude that the risk of infection is less when using a disposable needle guide in patients with additional co-morbidities. Although the number of patients was limited in our study; a reusable needle guide was found to be safe in patients who had additional co-morbidities.

Reprocessing instructions for transrectal biopsy equipment, such as a transducer, biopsy channel bracket, and needle guide, is well-defined in the Food and Drug Administration recommendations (19). The risks of transmission of hepatitis B virus, hepatitis C virus, human immunodeficiency virus, during prostate biopsies were evaluated by Lessa et al. (20). Although, on aggregate, their findings do not provide evidence of disease transmission, although they do not rule out transmission in some cases. We did not focus on viral transmission in this study. The needle guide can

be effectively disinfected with glutaraldehyde, but it must be disassembled from the transducer assembly before disinfection. We suggest that following the manufacturer's guidelines for the sterilization may be sufficient for using reusable instruments. The advantages of using a disposable needle guide are that it does not need to be reprocessed and it saves time, however, its cost is US\$ 5.00 per patient. Since the rate of infection appears to be same, whatever needle guide used, the issue of cost benefit ratio must always be kept in mind.

## CONCLUSION

It seems to be ineffective to reduce the infection rate after the prostate biopsy by using a disposable needle guide. Large scale and randomized studies are necessary to determine the effect of disposable needle guide on infection rate after TPNB.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

None declared.

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**EDITORIAL COMMENT**

Transrectal guided prostate needle biopsy (TPNB) is one of the most common outpatient diagnostic procedures in urology clinics and in this study the authors analyzed whether the use of disposable needle guide decrease the infectious complication after TPNB. Fever after prostate biopsy was developed in 3.5% patients (1). Urosepsis and bacteremia were rare but bothersome complications. Antibiotic prophylaxis including ciprofloxacin therapy has been administrated in most of the urology clinics to prevent infectious complications. Recently, Tuncel et al. suggested that the use of disposable needle guide could reduce the infection risk after prostate biopsy (2). However, in the current study the authors showed that it is ineffective to prevent infection.

Rutala et al. demonstrated that probe disinfection with glutaraldehyde greater than 2% concentration could be achieved when prostate needle guide was removed (3). Therefore, adequate cleaning and disinfection could explain the similar infection risks of use disposable and reusable needle guide. However, the small number of patients included in the study group prevents definite clinical judgment.

In spite of these controversially results, the disposable needle guide with a price of \$5.00 should be used for biopsy to overcome the difficulty in standardization of proper disinfection procedures in urology clinics. Whenever disposable needle is not available, mechanical cleaning to remove biologic material followed by 20 minutes of disinfection with glutaraldehyde should be performed after removing the reusable needle guide.

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**EDITORIAL COMMENT**

The authors should be commended on such a novel concept to potentially reduce infection after transrectal prostate needle biopsy. The methodology used to detect presence of infection was comprehensive and well designed. The randomized cohorts did not demonstrate a significant difference with regard to infection rates as a function of disposable versus

reusable needle guide. The bacteriologic infection rate was 4% in both groups while surprisingly, the symptomatic urinary tract infection rate was greater for the disposable needle guide.

Infection rates after transrectal biopsy are not negligible and certainly, any effort to reduce them should be explored. Our group has offered stereotactic

transperineal prostate biopsy (STPB) for patients that have had prior negative transrectal prostate biopsy despite continued elevation of PSA (1,2). While 40% of these patients are identified as having occult malignancy after STPB, an additional benefit has been a true null of post procedure infection. I acknowledge that STPB is not widely accepted as a first line biopsy technique, but given the high diagnostic yield and negligible risk of infection, STPB may be more commonplace in the future.

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# The Implication of Initial 24-Core Transrectal Prostate Biopsy Protocol on the Detection of Significant Prostate Cancer and High Grade Prostatic Intraepithelial Neoplasia

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## ABSTRACT

*Purpose:* To assess the diagnostic value of an initial 24-sample transrectal ultrasound guided (TRUS) prostate biopsy protocol compared to the 10-core technique.

*Materials and Methods:* We retrospectively reviewed the prostate biopsy database of consecutive men undergoing prostate biopsies under local anesthesia by using the 10 (Group A) and 24 (Group B) protocols. Men were stratified according to biopsy protocol and PSA levels. Exclusion criteria were age  $\geq 75$  years and PSA  $> 20$  ng/mL. The Mann-Whitney U and Fisher's exact test were used for statistical analysis.

*Results:* Between April 2007 and August 2009, 869 men underwent TRUS prostate biopsies of which 379 were eligible for the study. Group A (10-cores) consisted of 243 (64.11%) men and group B (24-cores) included 139 (35.89%) men. The overall prostate cancer detection rate was 39.09% and 34.55% in Group A and B, respectively ( $p = 0.43$ ). An overall 9.8% increase in Gleason 7 detection rate was found in Group B ( $p = 0.24$ ). The high-grade prostatic intraepithelial neoplasia (HGPIN) detection rate in men with negative initial biopsies was 15.54% and 35.55% in Group A and B, respectively ( $p < 0.001$ ). In patients with PSA  $< 10$  ng/mL, the 24-core technique increased Gleason 7 detection rate by 13.4% ( $p = 0.16$ ) and HGPIN by 23.4% ( $p = 0.0008$ ), compared to the 10 core technique. The 24-core technique increased the concordance between needle biopsy and prostatectomy specimen compared to 10-core technique ( $p < 0.002$ ).

*Conclusions:* The initial 24-core prostate biopsy protocol did not show any benefit in the detection of prostate cancer compared to the 10-core technique. However, it improved the HGPIN detection and the correlation between biopsy results and radical prostatectomy Gleason score in men with lower PSA levels.

**Key words:** *prostatic neoplasm; biopsy; Gleason score; prostatic intraepithelial neoplasia*

*Int Braz J Urol. 2011; 37: 87-93*

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## INTRODUCTION

As recommended by Hodge et al. (1), systematic transrectal ultrasound guided (TRUS) prostate biopsies is the principal method of diagnosing prostate cancer. Several studies have demonstrated that the traditional sextant technique may miss 15% - 31% of cancers and additional sampling from the

peripheral zone increases the diagnostic yield of prostate biopsies (2-5). Although there is still a matter of debate regarding the optimal number of cores taken at the initial prostate biopsy, several reports have shown that extended biopsy protocols involving  $> 10$ -cores have improved the diagnostic accuracy of clinically significant prostate cancer especially in patients with bigger glands (6,7) and also improved

the concordance of Gleason scores of needle biopsies and prostatectomy specimens (8).

The aim of the present study was to evaluate the incidence of prostate cancer, high-grade prostatic intraepithelial neoplasia (HGPIN) and perineural infiltration rates in men who had initial 24-core biopsies. The results were then compared with a similar group of men who had an initial 10-core prostate biopsy protocol. Men were categorized in different subgroups according to PSA levels. We also evaluated the ability of the initial saturation biopsy scheme to improve the prediction of the radical prostatectomy Gleason score compared to the 10-core technique.

## MATERIALS AND METHODS

We retrospectively reviewed the concurrently maintained database of consecutive men who underwent TRUS prostate biopsies at one referral center. Indications for biopsy were abnormal digital rectal examination (DRE) and elevated age specific PSA levels. The 10 cores and saturation (24 cores) biopsy protocols were used as initial techniques by two staff members of the department. We used a bi-plane 10 MHz transrectal probe (Pro-Focus 2202 TM,

BO-Medical, Denmark) with the capability of real time three-dimensional imaging. A 20 cm 18-gauge Chiba biopsy needle was used through a Pro-Mag™ automated ultra biopsy gun (Angiotech Vancouver, BC, Canada). Prostate biopsies were done with periprostatic nerve block by using 5 mL 0.5% marcaine mixed with 5 mL 1% lidocaine administered at the prostate base where the prostate sensory nerves enter the gland. One dose of ciprofloxacin as standard antibiotic prophylaxis was given to all patients prior to biopsy and written informed consent was obtained from all patients.

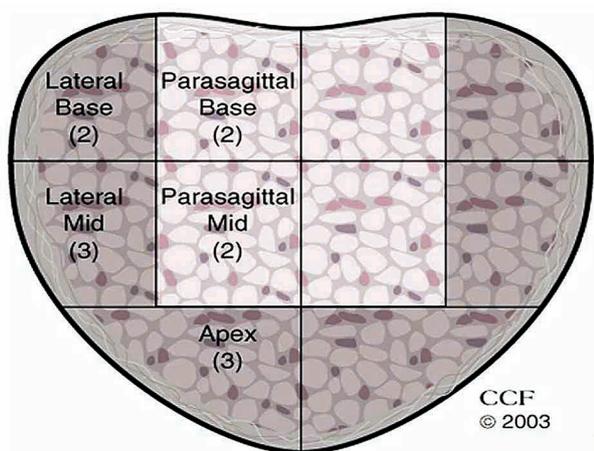
Men were categorized in two groups according to biopsy protocol and PSA levels. For group B (24 cores), the five sectors biopsied on each side were lateral base (2), lateral mid-zone (3), apex (3), parasagittal mid-zone (2) and parasagittal base (2), as shown in Figure-1. Men in group A (10 cores), had one biopsy core obtained from each of same sectors.

Men  $\geq 75$  years old, with PSA  $< 2.5$  ng/mL and/or  $> 20$  ng/mL and those who were previously biopsied, were excluded from analysis. Biopsy findings from both groups were compared regarding prostate cancer and HGPIN detection rates. Repeat saturation prostate biopsies were performed in 55 men from both groups with HGPIN in the initial biopsy. The concordance of Gleason score in the needle biopsy and prostatectomy specimens from both groups was also compared. Complications in both groups were recorded and compared. Results were analyzed using either the Mann-Whitney U test for continuous variables or Fisher's exact test for categorical variables.

## RESULTS

Between April 2007 and August 2009, 869 men were referred for TRUS needle prostate biopsies to one referral center. Overall, 379 men (clinical stage T1c, T2), were suitable for analysis. Group A (10-cores) consisted of 243 (64.11%) men and group B (24-cores) included 136 (35.89%) men. Both groups were comparable in terms of age, PSA and prostate volumes. Patient's demographics are summarized in Table-1.

The overall prostate cancer detection rate was 39.09% and 34.55% in Group A and B respectively



**Figure 1** – Template showing location of cores obtained in 24-core needle transrectal ultrasound biopsy. In the 10-core biopsy protocol, one core was obtained from each of the same sectors.

(p = 0.43). Table-2 shows prostate cancer detection rates according to biopsy protocol and PSA levels. An overall 9.8% increase in Gleason 7 score was found in Group B compared to Group A (p = 0.24). There was no difference in perineural infiltration rate between both groups (p = 0.79). At a PSA range between 2.6 - 9.9 ng/mL, the 24-core technique showed a non-statistically significant increase in Gleason 7 detection rate compared to the 10-core technique (p = 0.16). Table-3 shows Gleason score detection rates stratified according to biopsy protocol and PSA values.

The overall HGPIN detection rate in men with negative initial prostate biopsies was 15.54% and 35.55% in Group A and B, respectively (p < 0.001). In Group B and at a PSA range between 2.6 - 9.9 ng/mL the overall HGPIN detection rate was increased by 23.4% (p = 0.0008), compared to Group A. Multifocal HGPIN detection was 8.7% and 25.4% in group A and B, respectively (p < 0.001). After a follow-up of 6 to 13 months, prostate cancer was subsequently detected in 8% and 74% at repeat saturation biopsies of patients with isolated and multifocal HGPIN,

respectively. Table-4 shows HGPIN detection rates at different PSA levels stratified according to biopsy protocols.

Of the subset of 62 patients from both groups who underwent radical prostatectomy and were available for analysis, 13.7% had clinically insignificant cancer (maximal tumor dimension of 1.0 cm or less, Gleason sum 6 or less and organ confined disease at radical prostatectomy). In men who underwent 10 core biopsies, the overall rate of Gleason score upgrading after radical prostatectomy was 42.9% compared to 26.5% if 24 cores were taken (p < 0.002). No patients in the saturation needle biopsy group had a discrepancy of more than one Gleason unit in grade in the biopsy and surgical specimens. There were no differences in complication rates between both groups. Febrile urinary tract infections were recorded in three men from Group-B and in two men from Group A. While rectal bleeding necessitating admission was recorded in two men from Group B, there was no significant difference in patient discomfort between both groups.

**Table 1** – Clinical characteristics of patients.

Clinical Parameters	10-Biopsy Protocol (N = 243)	24-Biopsy Protocol (N = 136)	p Value
Age (years)	65.4 ± 6.4	66.1 ± 7.2	0.18
PSA (ng/ml)	6.2 ± 4.3	6.2 ± 3.9	0.20
Prostate volume (ml)	42.5 ± 5.2	46.7 ± 8.3	0.16
DRE(+)	21%	8.82%	0.028 NSS

DRE= digital rectal examination; NSS=not statistically significant.

**Table 2** – Prostate cancer detection rates according to biopsy protocol and PSA values.

PSA (ng/ml)	% PCa Detection		p Value (Fisher's exact test two-tailed)
	10-Biopsy Protocol	24-Biopsy Protocol	
2.6 - 9.9	37.05% (73/197)	33.66% (34/101)	0.61
10 - 20	47.8% (22/46)	37.1% (13/35)	0.37
2.6 - 20	39.09% (95/243)	34.55% (47/136)	0.43

PSA = prostate-specific antigen.

Prostate Cancer Detection and High Grade PIN

**Table 3** – Gleason score stratified according to biopsy protocol and PSA values.

Gleason Score	6		7		8		9	
Biopsy cores	10	24	10	24	10	24	10	24
	%		%		%		%	
2.6 - 9.9 ng/ml	49.3 (36/73)	41.2 (14/34)	21.9 (16/73)	35.3 (12/34)	4.1 (3/73)	11.8 (4/34)	8.2 (6/73)	2.9 (1/34)
10 - 20 ng/ml	63.6 (14/22)	46.15 (6/13)	59.0 (13/22)	53.8 (7/13)	18.2 (4/22)	15.4 (2/13)	9.0 (2/22)	7.7 (1/13)

PSA = prostate-specific antigen.

**Table 4** – High-grade prostatic intraepithelial neoplasia (HGPIN) detection rates in biopsy negative patients stratified according to biopsy protocol and PSA values.

PSA (ng/ml)	% HGPIN Detection		p Value (Fisher’s exact 2 tailed test)
	10-Biopsy Protocol	24-Biopsy Protocol	
2.6 - 9.9	16.9 (21/124)	40.3 (27/67)	0.0008
10 - 20	8.33 (2/24)	21.73 (5/23)	0.24

**COMMENTS**

Prostate cancer screening has currently increased the importance of prostate biopsy in urological practice and the detection of prostate cancer. Systemic transrectal needle biopsy of the prostate is the standard practice to detect the clinical stage and grade of disease, but controversy still exists about the optimal number of cores and the significance of HGPIN on first biopsy and how the biopsy results will improve the prediction of the prostatectomy Gleason score. In a review study, Epstein and Herawi recommended no repeat biopsies within the first year following the diagnosis of HGPIN, because the 24% median risk of prostate cancer diagnosis following detection of HGPIN was not higher than that of initial biopsy with benign disease (9). In our study, it was not the presence but the multifocality of HGPIN which was the strongest predisposing factor for detecting prostate cancer in a subsequent biopsy.

Presti (10) reviewed several studies evaluating several biopsy schemes and suggested that 10-12 core technique is optimal for most men undergoing initial prostate biopsy. Nesrallah et al. concluded that extended biopsy, with 14 cores, could improve prostate cancer detection rate compared to the sextant technique (11). Jones et al. noted, although in a small number of patients, that the 24 core technique as an initial strategy did not improve cancer detection (12).

While many studies show that saturation biopsy improves prostate cancer detection in patients with suspicious findings in a first negative biopsy, it does not seem to increase the cancer detection rate as an initial technique. Our findings are in agreement with these reports, as the 24 core initial biopsy technique did not improve the overall prostate cancer detection rate compared to the 10-core technique. In our study, men with PSA < 10 ng/mL who received an initial 24-core biopsy did not have a statistically significant increase in Gleason 7 detection rate when

compared to 10 core protocol at the same PSA level. Furthermore, there was no difference in Gleason 8 and 9 detection rates between both biopsy protocols.

Scattoni et al. also showed that the 18 core technique as an initial strategy demonstrated a higher cancer detection rate, although not statistically significant, than the 12 core protocol in men with PSA < 10 ng/mL, but they did not find any difference in the Gleason score (13). In a recent study, Scattoni et al. showed that both the number and site of cores have a great impact on prostate cancer detection and concluded that cancer detection rates increased with the increasing number of cores (14).

There are only few reports in the literature that address the influence of increased biopsy sampling on the detection rate of HGPIN and the cancer risk associated with it in subsequent biopsies. Epstein et al. report no relationship between the number of cores sampled and the incidence of HGPIN in needle biopsy (15).

However, Schoenfeld et al. found an incidence of 22% in HGPIN on the first saturation biopsy. This finding was confirmed in our study, where the HGPIN detection rate of 35.55% in men who had initial saturation biopsies was one of the highest reported in the literature (16).

Several studies have reported varying results for the positive predictive value of HGPIN as a single finding for prostate cancer detection in subsequent biopsies (17,18). In the present study, the cancer detection rate was significantly higher in patients with multifocal HGPIN in the initial biopsy, than in those with unifocal HGPIN ( $p = 0.001$ ). The majority of patients (78%) with multifocal HGPIN on initial saturation biopsy were diagnosed with prostate cancer on repeat saturation biopsy, of which 11.8% had clinically insignificant cancer in prostatectomy specimens. These findings have been confirmed by other studies where multifocality of HGPIN is an independent risk factor of prostate cancer in subsequent biopsies (19).

Recently, few reports have proved that the extended prostate biopsy scheme when compared to the sextant technique, significantly improves the correlation between needle biopsy and prostatectomy Gleason score, and reduces the risk of upgrading to a worse Gleason group at prostatectomy (20,21). In

our study, Gleason score upgrading was significantly higher in the 10-core protocol when compared to the saturation technique. This finding is important since most prostate cancer cases are now detected at an early stage and at a low PSA level. Leite et al. also, showed that extended prostate biopsies in men with PSA < 4 ng/mL increased the accuracy in tumor volume, Gleason score and stage, when comparing with higher PSA values (22).

No difference in the detection of clinically insignificant cancer in radical prostatectomy specimens was observed between both biopsy protocols. In addition to its interesting results, the present study presents some limitations with the most obvious being that we do not know how many cancers were missed with either the 24 or 10 core technique. Thus, our study is influenced by verification bias because we cannot define the real diagnostic accuracy of our biopsy schemes. Another limitation is that this study is a retrospective audit with a non randomized design.

The present study did not show a real benefit for the saturation biopsy protocol as an initial technique for the detection of prostate cancer. However, it did show that an initial 24-core technique increased the detection of multifocal HGPIN and improved the concordance of Gleason grading between needle biopsy and radical prostatectomy specimen, which is crucial in therapeutic decision-making based on needle biopsy.

## CONCLUSIONS

Our findings add to the growing evidence in the literature that an initial saturation (24-core) prostate biopsy protocol does not improve the overall cancer detection rate compared to the 10-core technique. Although 24-core prostate biopsy technique improved the sensitivity of HGPIN detection especially in men with PSA levels less than 10 ng/mL, it cannot be justified as the standard initial biopsy technique. Patients with multifocal HGPIN on initial saturation biopsy certainly warrant repeat saturation biopsy since the great majority of them will be later diagnosed with prostate cancer. Given the fact of its safety profile, the 24-core prostate biopsy protocol could probably be proposed as the initial technique

for a selected group of patients, such as younger men with lower PSA levels who are candidates for curative treatment, or younger patients who have opted for active surveillance. Further studies are certainly needed in this field.

## CONFLICT OF INTEREST

None declared.

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## EDITORIAL COMMENT

The search continues for the optimal number of prostate biopsies to maximize clinical utility while minimizing complications. The authors reported on a non-randomized group of 379 men who underwent transrectal prostate biopsy using either a 10 or 24-core technique. No increased complications were reported with the saturation technique. The detection of prostate cancer (including Gleason grade 7) was not statistically different between the two groups while HGPIN was increased. A prior thorough review publication (1) reported a median risk recorded in the literature for cancer following the diagnosis of HGPIN on needle biopsy is 24.1%, which is not much higher than the general population and recommended against rebiopsy based solely on HGPIN. The authors in the current study report improved concordance between biopsy and prostatectomy specimens when

more biopsies were taken. In the face of no increased cancer detection, the urologist must balance the impact of potential increased complications, time, and patient discomfort when deciding on prostate biopsy technique.

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## Infrapubic Approach for Malleable Penile Implant

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### ABSTRACT

*Purpose:* Today, we find that the implant of malleable prostheses still plays a leading role in the surgical treatment of erectile dysfunction. These may involve patients for which the cosmetic advantages of inflatable devices are not as important as low cost, the easier use and less incidence of mechanical complications in the malleable implants. This paper demonstrates infrapubic approach as a technical option for this kind of implant.

*Surgical Technique:* It offers technical resources and emphasizes the facility in using the method, reducing cutaneous exposure, which diminishes risks of contamination.

*Comments:* As occurs in inflatable implants, when implanting malleable prostheses through the infrapubic access, care must also be taken regarding the possibility of lesion to the vascular-nervous bundle. On the other hand, the approach through the dorsal surface of the corpora cavernosa has a natural capacity for anatomical protection of the urethra, not requiring transurethral catheterization. This benefit is of the utmost importance when considering possible causes of per and postoperative morbidity.

Accordingly, we can consider that the infrapubic approach is an effective method and prevails as a technical option for implanting malleable prostheses.

**Key words:** *erectile dysfunction; penile prosthesis; urologic surgical procedures, male*  
*Int Braz J Urol. 2011; 37: 94-9*

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### INTRODUCTION

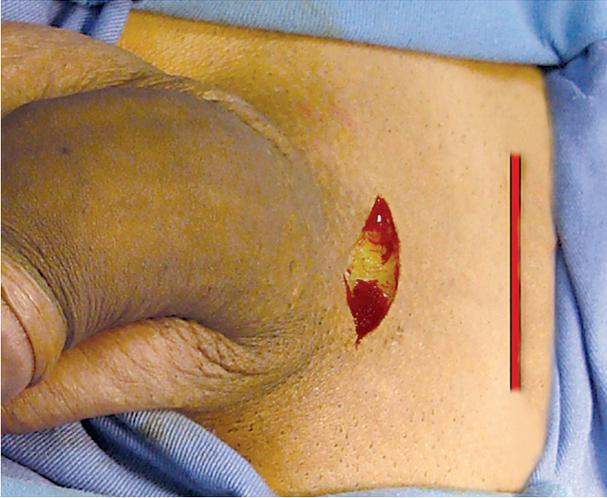
Since 1936 when Nikolaj Bogaraz reconstructed an amputated penis using a tubular abdominal graft in which he inserted a section of rib cartilage, the search for ideal materials and techniques for penile implants has been continuous. Over the years, acrylic, polyethylene, silastic, silicon rubber and other prostheses have been used, whether for rigid, articulated, malleable and later inflatable of one, two or three-piece constitution (1,2).

Currently, malleable prostheses available in the market are quite similar to each other, with a central structure consisting of steel or silver filaments covered by two or more layers of silicon sheath. They

all offer various modalities of size adjustment, by cutting or adding extensors to their proximal portion.

Although today patients and surgeons prefer inflatable prostheses, some circumstances may require the malleable implant. These may involve patients for which the cosmetic advantages of inflatable devices are not as important as low cost, the easier use and less incidence of mechanical complications in the malleable implants (1-6).

With regard to the surgical technique, various approaches have been described for implanting penile prostheses: the dorsal subcoronal, penile proximal, longitudinal penoscrotal, transverse penoscrotal perineal and combined incisions (7). More recently, a minimally invasive infrapubic approach was proposed



**Figure 1** – Suggested incision. The red line sets the relation with the infrapubic incision proposed in the minimally invasive technique described for the three-piece inflatable implants.

for the implant of a three-piece inflatable prosthesis (8). The name used comes from the fact of making a single transverse incision below the pubis. The pur-

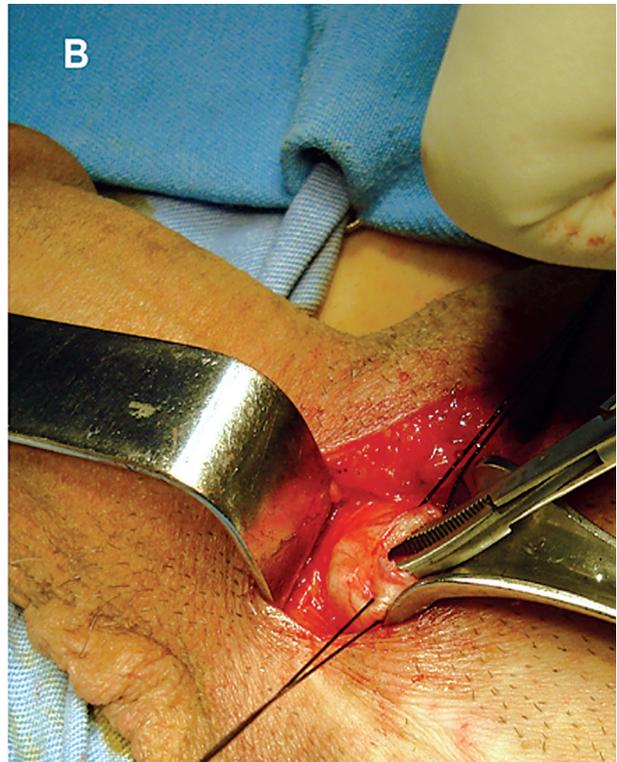
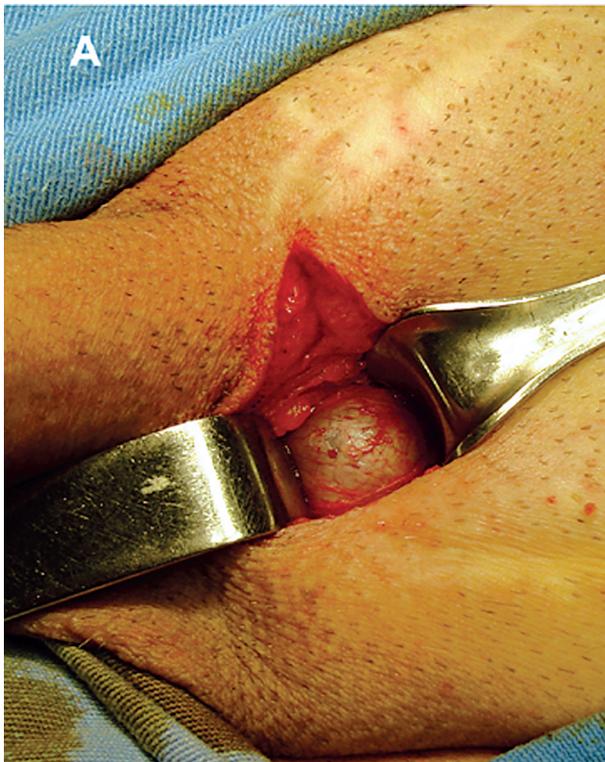
pose of this paper is to demonstrate the ease of this approach for the implant of malleable prostheses.

## SURGICAL TECHNIQUE

The infrapubic approach adopted in our hospital is characterized by a two to three centimeter transverse incision, approximately one centimeter from the base of the penis (Figure-1).

Skin and subcutaneous tissue are incised using a conventional scalpel. Of course, care must be taken to prevent lesions both to the suspensory ligament of the penis and to the medial neurovascular bundle. With this in mind, the dissection is deepened using scissors, staying at each angle of the incision and thus keeping away from its center.

The corpora cavernosa are easily visible by a simple thrust of the penile axis. This procedure causes stretching and shrinkage of the corpora cavernosa, facilitating its identification and subsequent dissection (Figure-2A).



**Figure 2** – Identification and incision of the corpus cavernous.



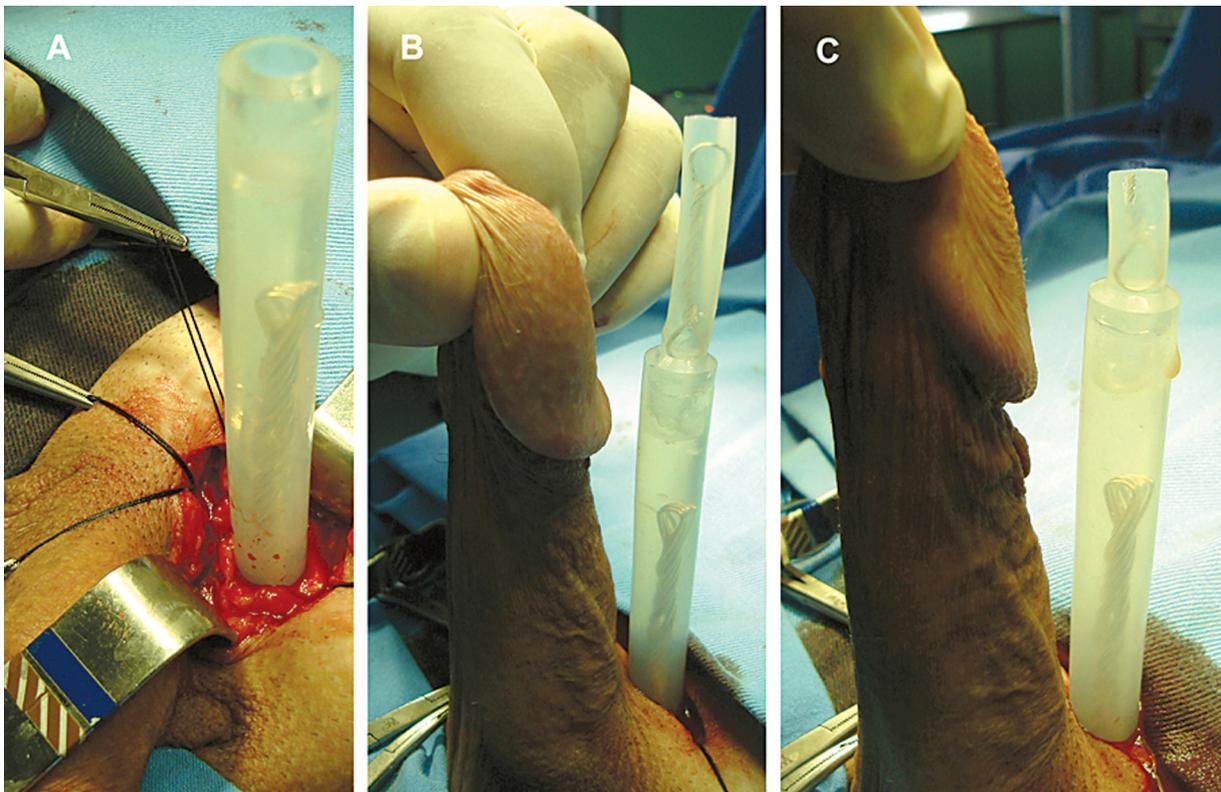
**Figure 3** – Cavernotome.

A small longitudinal incision on the dorsal surface of the corpus cavernous is made using a conventional scalpel between stay sutures. The erectile tissue is pushed down using Halsted forceps and the incision is extended to its two angles (Figure-2B).

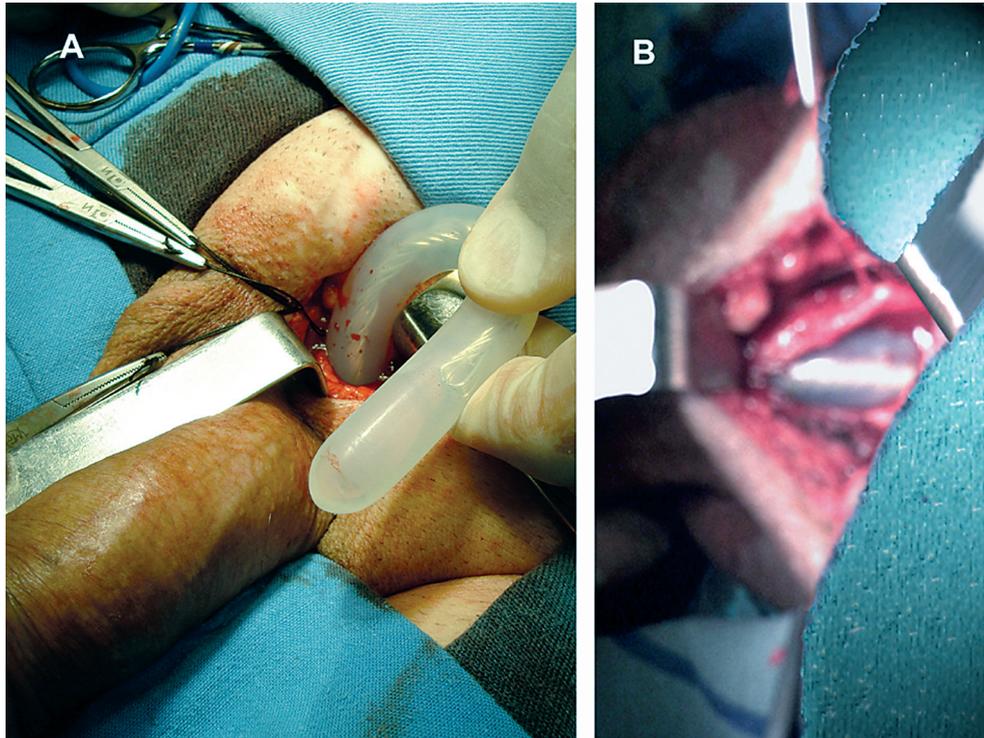
The progressive dilation of the corpus cavernous is made using Heggar dilators in the proximal and distal directions, as described for the other approaches.

In cases where any adhesences or fibrosis of the cavernous tissue hamper the dilation of the corpora cavernosa, several technical resources have been proposed (9-11). In such cases, in our Hospital, this dilation is mostly done by using a cavernotome developed by the urological unit. This instrument is characterized by a grip with a distal cylindrical end containing cutting spiral grooves (Figure-3). The grooved surface is considerably more effective than that of the dilators and file used previously. Its use consists of small delicate rotational and longitudinal movements in order to remove the portion of the cavernous tissue with fibrosis, pushing the rest down. It should be mentioned that the purpose is to “file” and not “pull out” the tissue. Extreme care must be taken when using the instrument, especially at the start of apprenticeship.

We used the following procedure to adapt the size of the prosthesis: first, it is introduced inverted in the proximal direction. Next, the maximum extension of the penis will determine the size of the



**Figure 4** – Procedure to adapt the size of the prosthesis.



**Figure 5** – Prosthesis position.

prosthesis. The section of the cylinder or adaptation with extensors is done by taking as reference the height corresponding to half the glans. The cylinder is then removed and replaced in its normal position. In our experience with this measuring method, when the prosthesis is introduced into its final position, the natural angulation of the corpus cavernosum, at the base of the penis, adjusts perfectly to the prosthesis without requiring further corrections (Figure-4).

Before finally inserting the prosthesis, the entire process described herein above is repeated on the contralateral side.

This approach also involves the well-known resource of the loop curvature of the cylinder that especially facilitates its distal insertion and prevents deformities caused by angulations resulting from nudging the metal filament (Figure-5).

The synthesis of tunica albuginea is accomplished with a 3-0 continuous absorbable synthetic suture. Hemostasis is reviewed using diathermo-coagulation and the other incision planes are closed with a 3-0 absorbable synthetic suture. Skin incision is closed in a continuous or subcuticular 5-0 absorb-

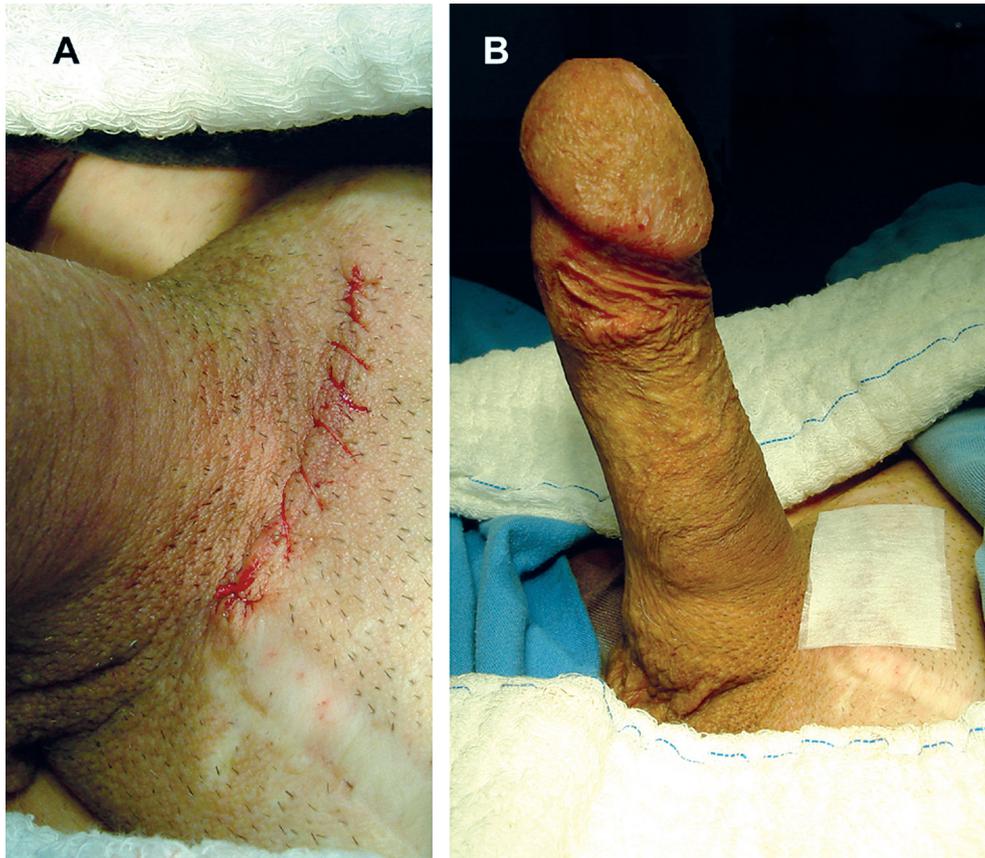
able synthetic suture, in order to prevent the patient's discomfort when removing the suture (Figure-6A).

We only use an occlusive sterile surgical paper tape, since the careful review of hemostasia does not require larger compressive dressings that are, in fact, in this approach, of very little help (Figure-6B).

The proposed approach is being adopted in both primary surgery and reoperations. In such cases, it is fully in accordance with the basic principles of surgical interventions that recommend that the approach adopted in a region already previously manipulated is, whenever possible, through a fibrosis-free area. Accordingly, in the cases of revisions or reimplants of malleable prostheses, where the first operation was done through a penoscrotal approach, we consider the infrapubic approach to be first option in another intervention.

## COMMENTS

The proposed approach as a technical option for the implant of malleable prostheses finds sup-



**Figure 6** – Final aspect.

port when we consider that despite the advances in the technology of inflatable implants, the malleable prostheses are still used. This fact is due not only to the technical facility of its implantation and less risk of mechanical failure, but also mainly due to the much lower surgical cost (1-6).

The infrapubic approach has therefore been adopted in our hospital since 2007, also as a technical option for malleable penile implants. Considering how simple this approach is, it has practically totally substituted the longitudinal penoscrotal approach that we previously used.

Taking the three-piece inflatable prostheses as reference, today the penoscrotal approach is being widely used by surgeons, tending to substitute the infrapubic incision used previously in such procedures (2,12). However, in recent years, a minimally invasive technique retrieves the infrapubic approach as an option for the three-piece inflatable implants (8).

Similarly, with regard to malleable prostheses, although a kind of infrapubic approach has been mentioned since 1976 by Kelâmi, we can state that, at present, this type of access is seldom addressed in medical literature, while the penoscrotal approach is more often mentioned by the surgeons (1,2,7). Nevertheless, the infrapubic approach is also an excellent technical option in these cases (13-16).

When implanting the inflatable prostheses, the main benefit of the infrapubic approach is the possibility of direct vision for implanting the liquid reservoir. Its disadvantages include limited corpus cavernos exposure and difficulty in anchoring the pump in the scrotum. Although lesions of the dorsal nerves of the penis seldom occur during this procedure, it is a risk to be considered in the dissection to expose the corpora cavernosa. The benefits of the penoscrotal approach include better exposure of the corpus cavernos, impossibility of damaging dorsal nerves of the penis and

more facility in anchoring the inflating pump. Its main disadvantages are more possibility of urethral lesion and blindly implant of the reservoir in the retropubic space (17).

As occurs in inflatable implants, when implanting malleable prostheses through the infrapubic access care must also be taken regarding the possibility of lesion to the vascular-nervous bundle. On the other hand, the approach through the dorsal surface of the corpora cavernosa has a natural capacity for anatomical protection of the urethra, not requiring transurethral catheterism. This benefit is of the utmost importance when considering possible causes of per and postoperative morbidity (18).

Accordingly, we can consider that the infrapubic approach is an effective method and prevails as a technical option for implanting malleable prostheses.

For obvious reasons, the benefits and disadvantages must be carefully considered in obese patients with extensive adipose panicle in the region to be cut.

## CONFLICT OF INTEREST

None declared.

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# Urodynamics in Women from Menopause to Oldest Age: What Motive? What Diagnosis?

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## ABSTRACT

*Purpose:* To analyze age-associated changes as a motive for urodynamics and urodynamic diagnosis in community-dwelling menopausal women and to discuss the role of menopause and ageing.

*Materials and Methods:* Four hundred and forty nine consecutive menopausal women referred for urodynamic evaluation of lower urinary tract (LUT) symptoms, met the inclusion criteria and were stratified into 3 age groups: 55-64 years (A), 65-74 years (B), and 75-93 years (C). Comprehensive assessment included previous medical history and clinical examination. Studied items were motive for urodynamics, results of uroflows (free flow and intubated flow) and cystometry, urethral pressure profilometry, and final urodynamic diagnosis.

*Results:* The main motive was incontinence (66.3%) with significant increase of mixed incontinence in group C ( $p = 0.028$ ). Detrusor function significantly deteriorated in the oldest group, mainly in absence of neurological disease (overactivity  $p = 0.019$ ; impaired contractility  $p = 0.028$ ). In the entire population, underactivity predominated in group C ( $p = 0.0024$ ). A progressive decrease of maximum urethral closure pressure occurred with ageing. In subjects with no detrusor overactivity there was a decrease with age of detrusor pressure at opening and at maximum flow, and of maximum flow while post void residual increased only in the C group.

*Conclusion:* In our population of community-dwelling menopausal women, incontinence was the main motive for urodynamics increasing with ageing. A brisk change in LUT function of women older than 75 years underlined deterioration in bladder function with a high incidence of detrusor hyperactivity with or without impaired contractility while change in urethral function was progressive. Effect of ageing appears to be predominant compared to menopause.

*Key words:* ageing; women; LUTS; urodynamics

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## INTRODUCTION

Lower urinary tract (LUT) dysfunction is a major cause of reduced quality of life in the ageing population. For women the postmenopausal period has significantly increased and is now up to one third or more of the total lifespan. LUT function is affected by estrogen withdrawal and ageing. A major consequence of estrogen withdrawal is urogenital atrophy

with possible contribution to urinary symptoms such as frequency, urgency and incontinence (1). Ageing is associated with a progressive decrease in autonomic innervation and of detrusor contractility (2,3). Some studies have focused on identifying the effects of menopause and ageing (4-6) on lifestyle. In spite of a reported significant trend for increased prevalence of symptoms with ageing, none of these studies have identified causes.

Despite the fact that many patients avoid discussing their problems, postmenopausal women constitute a large population who undergo urodynamics for lower urinary tract symptoms (LUTS) and urodynamics is considered as the best tool for the evaluation of patients with LUTS.

Some authors (7) have concluded that female bladder and urethral function deteriorate throughout adult life, whether or not detrusor overactivity (DO) is present. In a previous study (8) we analyzed the motive for urodynamics and the urodynamic diagnosis in a population of community-dwelling elderly females (80+ years); we showed that incontinence was the main motive and DO the main diagnosis.

Our objectives in this study were to extend our analysis to a large population of postmenopausal community-dwelling women referred as outpatients for evaluation of LUTS and to consider the relationships between menopause and ageing on the changes in the motive of referral and in LUT function.

## MATERIALS AND METHODS

The population consisted of 449 consecutive women, community-dwelling, aged  $\geq 55$  years who underwent urodynamics for LUTS in our outpatient urodynamics clinic between January 2005 and March 2008. Patients were stratified in 3 age groups: 55-64 years (A, short-term menopause), 65-74 years (B, middle-term menopause), and 75-93 years (C, long-term menopause). The lowest age group (55 years) was set so that the women were all postmenopausal (in France, the mean age of menopause is 50.1 years). This retrospective study was conducted in accordance with the declaration of Helsinki. The local practice of our Ethics Committee does not require a formal institutional review board approval for retrospective studies.

Urodynamics investigations were performed according to Good Urodynamic Practices (GUP) (9) using the Laborie's Dorado® unit. Detailed urodynamic session included one initial free uroflow (FF1), cystometry and pressure-flow study (PFs) in a seated position, urethral pressure profilometry (UPP) in supine position, bladder empty before cystometry and

bladder filled (according with the functional bladder capacity) after PFs and then a second FF. Cystometry was performed with a 7F triple-lumen urethral catheter. Bladder was filled with saline at room-temperature at a medium filling rate of 50 mL/min. Abdominal pressure was recorded using a punctured intra-rectal balloon catheter.

Pressures were zeroed to atmosphere with the transducers placed at the level of the upper edge of the symphysis pubis.

No routine provocative manoeuvres for DO were performed but according to GUP coughs were used as quality control of pressure recordings (9).

All patients had an evaluation including medical history and usual medication, bladder diary for at least 48 hours including voiding times and voided volumes during day and night-time, physical examination and dipstick urinalysis.

Specific evaluation comprised of a history of LUTS, previous history of neurological disease (stroke, multiple sclerosis, lumbar injury, etc.) or dementia, pelvic floor status and previous pelvic surgery. Patients with LUTS due to a specific physiopathology (complete spinal cord injury) were excluded, as well as those who were unable to perform the standardized protocol for complete retention (no FF and PFs were possible) or severe dementia (involving failure to understand simple orders or Mini Mental State  $< 20$ ).

Two physicians independently assessed urodynamics; good agreement occurred in up to 95% of the files. In the remaining 5%, a third interpretation was carried out jointly to agree on a single conclusion. Studied items were motive for urodynamics, feasibility of uroflows (FF and PFs), detrusor behavior during filling cystometry, UPP and final urodynamic diagnosis. Feasibility of uroflows was defined by a voided volume higher than 100 mL. To analyze the detrusor behavior during filling cystometry, an additive stratification was used with the following parameters: age (A,B,C), without neurological disease (I) or with (II) (was verified that previous pelvic surgery did not lead to significant difference).

Quality of life was assessed using the ICIQ-UI-SF questionnaire for incontinent patients (10) and visual analog scale (VAS) for continent patients.

**Statistical Analysis**

Data are presented as mean ± SD and range. The Wilcoxon signed rank test was used for comparison of related samples, analysis of variance and the chi-square test to compare unrelated samples. Statistical analysis was performed using SAS, version 5.0 (SAS Institute, Inc., Cary, NC). All statistical results were considered significant at  $p < 0.05$ .

**RESULTS**

**Population**

The 3 sub-groups were homogeneous in terms of numbers of patients: A = 137, B = 155, C = 157. Mean age was  $59 \pm 3$  years in A,  $70 \pm 3$ y in B and  $81 \pm 4$  years in C.

Oral or transdermal hormone replacement therapy (HRT) was respectively taken by 11 (8.0%) women in A and 29 (18.8%) in B; in C, 15 women (9.6%) received estrogen locally.

**Motive for Urodynamics**

Table-1 lists the motive for urodynamics by age-groups. Incontinence was the main motive, evoked by 298 (66.3%) patients. Mixed incontinence

increased with ageing with a significant difference between groups A and C ( $p = 0.028$ ).

ICIQ-SF score (maximum 21) and VAS score (maximum 10) are detailed in Table-2.

**Previous History**

Previous history of medical disease or/and pelvic surgery was obtained by detailed questioning, and is listed in Table-3.

One hundred and sixteen (25.8%) patients had a previous history of neurological disease (A = 35; B = 36; C = 45) and 151 (33.6%) had undergone previous pelvic surgery (A = 56; B = 54; C = 41).

Eleven patients were referred for pre-operative evaluation of pelvic organ prolapse (POP); POP grade 2-3 was revealed during urogenital examination in 31 additional patients (A = 9; B = 13; C = 9).

**Feasibility of the Tests**

The percentage of interpretable initial FF was significantly higher in age-group B (A = 57.8%; B = 69.3%; C = 47.5%) while there was not a significant difference between the age groups for both interpretable PFs (A = 64.2%; B = 56.1%; C = 56.4%) and FF at end of the session (A = 94.6%; B = 94.8%; C = 97.2%).

*Table 1 – Motive for urodynamics. POP = pelvic organ prolapse.*

Complaint	A (55-64 years)	B (65-74 years)	C (≥ 75 years)	Total	
Incontinence	Stress	20	28	21	122
	Urge	41	42	39	122
	Mixed	23	36	48	107
Number of incontinent	84 (61.3%)	106 (68.4%)	108 (68.8%)	298	
Frequency	22	26	18	66	
Dysuria	8	8	6	22	
Chronic incomplete retention	3	6	14	23	
Pre-operative (POP)	3	6	2	11	
Various (pain, infection, etc.)	17	3	9	29	
Number of continent	53	49	49	151	

**Table 2** – Quality of life in the studied population. ICIQ-UI-SF = International Consultation on Incontinence Questionnaire on Urinary Incontinence Short Form; VAS = Visual Analog Scale.

	A (55-64 years)	B (65-74 years)	C (≥ 75 years)	p Value
ICIQ-UI-SF	12.8	10.9	11.0	n.s.
VAS	5.1	5.0	4.5	n.s.

n.s. = not significant.

**Table 3** – Previous medical history of the studied population.

Previous History	A (55-64 years)	B (65-74 years)	C (≥ 75 years)
Neurological disease	35	36	45
Cognitive impairment (Mini Mental State ≥ 20)	5	0	19
Pelvic surgery			
Pelvic organ prolapse	5	5	3
Hysterectomy	17	17	13
TVT or sling	23	29	19
Cure of incontinence	11	3	6
Other diseases			
Musculo-skeletal	29	45	69
Cardio-vascular	13	77	83
Depression	24	16	24
Diabetes mellitus	13	22	15

TVT = tension free vaginal tape.

### Cystometry (Table-4)

Detrusor overactivity (involuntary detrusor contraction during the filling phase, DO) (9-11) and its subset detrusor hyperactivity with impaired contractility (DHIC) (12) were found in a total of 142 patients (32%) with a significant increase in group C: 43% vs. 23% A & 30% B ( $p = 0.0004$ ); detrusor underactivity (impaired detrusor contraction leading to prolonged voiding time and high residual volume) (DUA) (9) was found in 62 patients (14%) with also a significant increase in C ( $p = 0.0024$ ). Normal detrusor behavior significantly decreased in C ( $p = 0.005$ ).

In sub-group I (333 patients without neurological disease) the detrusor behavior was normal in 194 (58.2%) with only a significant difference between subgroups I-B and I-C ( $p = 0.044$ ). DO and

DHIC significantly increased in subgroup I-C (respectively  $p = 0.019$  and  $0.028$ ) but the increase in DUA was not significant.

In subgroup II (116 patients with neurological disease) the detrusor behavior was normal in 33 (28.4%). DO was found in 46 (39.6%), DHIC in 15 (12.9%) and DUA in 20 (17.2%). There was no significant difference between the 3 age groups regarding DO: II-A (45.7%), II-B (36.1%) and II-C (37.7%). An increase in DHIC and DUA in subgroup II-C was observed.

Functional bladder capacity (FBC) did not change significantly with age but depended on DO (Table-5). Some other voiding parameters were modified in DO patients:  $p_{det.op}$  and  $p_{det.Qmax}$  increased, the voiding time decreased, except in group A, and PVR was lower in group C. In the DO population,  $p_{det.op}$  was higher than  $p_{det.Qmax}$ .

**Table 4** – Changes in uroflow parameters comparing free uroflow (FF) and pressure-flow study (PFs).

	A (55-64 y)		p	B (65-74 y)		p	C (≥ 75 y)		p
	FF1	PFs		FF1	PFs		FF1	PFs	
Q <sub>max</sub> (mL/s)	23 ± 11	14 ± 8	<0.0001	19 ± 11	14 ± 7	<0.0001	13 ± 8	10 ± 5	0.0358
V <sub>voided</sub> (mL)	256 ± 154	320 ± 159	0.007	249 ± 150	333 ± 147	0.0008	124 ± 122	233 ± 143	<0.0001
PVR (mL)	34 ± 74	77 ± 117	0.007	59 ± 96	101 ± 142	0.0004	74 ± 121	129 ± 143	<0.0001
t <sub>void</sub> (s)	27 ± 19	64 ± 48	<0.0001	34 ± 26	66 ± 42	<0.0001	27 ± 25	61 ± 49	<0.0001

**Uroflow Parameters (Table-6)**

Maximum flow rate diminished with age whether measured during FF or PFs, and was significantly lower during PFs. The decrease was independent of DO. Post void residual (PVR) significantly increased only in group C.

**UPP (Table-7)**

Maximum urethral closure pressure (MUCP) decreased steadily with age remaining in the range of the “theoretical” value which is bladder filled (110 - age) ± 20% in cm H<sub>2</sub>O (13).

MUCP was non significantly higher in continent patients either with bladder empty or bladder filled, but was significantly lower bladder filled vs. bladder empty in incontinent whatever the age and incontinent in group B.

**Urodynamic Diagnosis**

Detrusor hyperactivity (DO or DHIC) was the main urodynamic diagnosis increasing signifi-

cantly in group C: 68/157 (43%) vs. 38/137 (27%) (A) and 36/155 (23%) (B) (p = 0.0004) whatever the neurological status. DO was significantly more frequent (p = 0.007) in the age-group C (28%) vs. A (23%) and B (15%) and DHIC increased with ageing: 4% in A, 8% in B and 15% in C.

DUA was predominant in the oldest group 34/157 (22%) compared with 14/137 (10%) (A) and 14/155 (9%) (B). That dysfunction was associated with an incompetent sphincter in 2 A patients, 5 B and 14 C.

Intrinsic sphincter deficiency (ISD) was predominant in B 56/155 (36%) vs. A 34/137 (25%) or C 38/157 (24%).

Low bladder compliance (≤ 20 mL/cm H<sub>2</sub>O) was predominant in group B: 10 women of which 9 were without neurological disease.

Normal urodynamic tests were observed in 31 (22%) A patients, 24 (15%) in B and 18 (11%) in C.

Various or uncertain diagnoses were more frequent in A (16%) and B (14%) than in C (6%).

**Table 5** – Detrusor behavior vs. age and neurological status. DO = detrusor overactivity; DHIC = detrusor hyperactivity with impaired contractility; DUA = detrusor underactivity; LC = low bladder compliance; N = normal.

	DO			DHIC			DUA			LC			N		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
I without neurological disease	16	10	27	3	10	15	10	10	22	5	9	2	69	79	46
II with neurological disease	16	13	17	3	3	9	4	4	12	0	1	1	12	15	6
Number of patients	32	23	44	6	13	24	14	14	34	5	10	3	81	94	52

**Table 6** – Influence of detrusor overactivity (DO) on the urodynamic parameters during pressure-flow study (PFs).

	A (55-64 years)			B (65-74 years)			C (≥ 75 years)		
	DO	no DO	p	DO	no DO	p	DO	no DO	p
FBC (mL)	288 ± 119	407 ± 123	<0.0001	314 ± 124	436 ± 125	0.0005	289 ± 128	427 ± 128	<0.0001
V <sub>voided</sub> (mL)	237 ± 119	353 ± 154	0.0004	231 ± 101	362 ± 145	0.0004	198 ± 130	274 ± 147	0.0074
Q <sub>max</sub> (mL/s)	13 ± 7	15 ± 8	n.s.	12 ± 6	15 ± 8	n.s.	10 ± 5	11 ± 6	n.s.
PVR (mL)	71 ± 98	80 ± 124	n.s.	119 ± 111	96 ± 149	n.s.	87 ± 88	175 ± 174	0.015
p <sub>det.op</sub> (cm H <sub>2</sub> O)	29 ± 20	17 ± 14	0.0012	30 ± 24	14 ± 12	0.0022	26 ± 18	13 ± 16	<0.001
p <sub>det.Qmax</sub> (cm H <sub>2</sub> O)	27 ± 11	23 ± 13	n.s.	29 ± 19	21 ± 14	0.0032	24 ± 14	15 ± 13	0.0011
t <sub>void</sub> (s)	66 ± 67	63 ± 38	n.s.	49 ± 25	70 ± 45	n.s.	49 ± 36	73 ± 57	n.s.

n.s. = not significant.

**Table 7** – Maximal urethral closure pressure (MUCP) vs. age and continence status.

MUCP cm H <sub>2</sub> O	A (55-64 years)		B (65-74 years)		C (≥ 75 years)	
	continent	incontinent	continent	incontinent	continent	incontinent
Bladder empty	70 ± 28	62 ± 26	56 ± 24	52 ± 23	50 ± 27	43 ± 18
Bladder filled	62 ± 28	55 ± 28	45 ± 24	44 ± 22	39 ± 21	35 ± 18
p	0.07	0.0008	0.003	0.0002	0.07	<0.0001
“theoretical” value bladder filled	38-62		30-50		24-36	

## COMMENTS

This study was retrospective and therefore has its own limitations. However, we used a standardized protocol for urodynamics and all files contain the same items. The population is representative of community-dwelling women with urinary disorders and age-groups are homogeneous in the number of patients.

In our postmenopausal population, urinary incontinence (UI) was the main motive for urodynamics with a percentage variation between 61.3 and 68.8. These values, above the estimated prevalence of urinary incontinence in middle-aged and older women (4), resulted from our recruitment, i.e. women referred for evaluation of LUT dysfunction. In the general population many patients avoid discussing problems related to incontinence, lowering the recorded per-

centages. Prevalence of urinary incontinence during the menopausal transition has been reported with a variation from 8% to 56%; nevertheless, evidence that menopause is an independent factor in the prevalence of incontinence remains lacking (4).

Mixed UI increases with ageing, probably due to the association of a decreased urethral sphincter function and occurrence of detrusor overactivity.

Urge incontinence does not vary significantly with age. On the other hand, stress incontinence appears as slightly predominant in age-group B in patients who take oral or transdermal HRT (or who have taken it five to ten years after menopause); this is consistent with the findings of Steinauer et al. (14) who report an increased risk for stress incontinence in women taking HRT.

Quality of life scores show that the impact of LUT dysfunction remains stable with age.

Achievement of interpretable tests, requiring a “comfortable” environment and some relaxation is often difficult at the beginning of the session.

As previously reported (7) FBC does not diminish with age and is smaller, with no variation with age, in DO subjects.

There are some surprising results as the subgroup B differs from the others in terms of normal detrusor behavior, low occurrence of DO and low bladder compliance. One plausible explanation may be the higher incidence of stress incontinence in this group.

DO increases with age regardless of a history of neurological disease or previous pelvic surgery. In the entire DO population,  $p_{det,op}$  is higher than  $p_{det,Qmax}$  which may imply a common finding of an incomplete sphincter relaxation at the onset of flow.

DHIC, is a common condition in frail elderly individuals (12), and DUA increases in the same way; these two latter behaviors lead respectively to UI with high PVR and to chronic retention. The decrease of detrusor contractility with ageing can be related to the decrease in caveolae, bladder weight and smooth muscle density with age (3).

For a complaint consistent with bladder overactivity (urge or mixed incontinence, frequency) similar percentage (near 85%) in DO plus DHIC is found in the 3 age-groups.  $Q_{max}$ ,  $p_{det,op}$  and  $p_{det,Qmax}$  all decline with age in women without DO. This observation is consistent with previous studies which show age-associated deterioration of the detrusor contractility (15,16). However, decreased contractility allows an effective emptying except in the oldest age-group where PVR increases.

MUCP decreases with age, a result consistent with previous studies (7); with the bladder filled, the values are in the range of the “theoretical values” (13). Perucchini et al. (17) reported that this decrease could be the reflect of the association with age of a loss of striated muscle in the female urethra.

In incontinent women, the decrease observed between bladder empty and bladder filled demonstrates a lack of adaptation of the urethral sphincter to bladder filling. This behavior could be explained by both sphincter sarcopenia and impaired pelvic floor.

An unexpected and unexplained finding is the significant decrease of MUCP bladder filled in continent women of the middle age-group.

For a complaint consistent with an impaired sphincter function (stress or mixed incontinence), a lower urethral closure pressure than expected for age was found in only 52.6% (A), 57.4% (B) and 62.7% (C).

Urodynamic diagnosis was found in a high percentage (90% or more) of the 3 age groups.

Abnormal detrusor behavior appears as the main final diagnosis with specific changes according to ageing. In the oldest women without neurological disease, a significant increase of DO, DHIC was observed; the increase of DUA was not considered significant. The incidence of DHIC and DUA in this age group is more likely related to decreased  $p_{det,op}$  and  $p_{det,Qmax}$  leading to an increased PVR.

In all groups, complaint of stress and urge incontinence was respectively associated with ISD and detrusor hyperactivity (DO or DHIC). Mixed incontinence was associated with ISD in age-groups B and C and with detrusor hyperactivity in C.

One final question: Can the responsibility of the changes in LUT function be attributed to the normal ageing process or to menopause?

Although menopause has been shown to be associated with urinary incontinence, evidence for it being an independent factor in the prevalence of urinary incontinence and bladder dysfunction remains lacking. In our population, menopause and ageing could be considered as independent factors as the percentage of women taking HRT is insignificant. Brisk changes in LUT function occurred in the oldest group while for the two other age groups (A and B) changes were progressive. Note that the change in urethral function is progressive with ageing. Therefore, if the role of menopause can be considered in younger and middle age, we propose that the role of ageing is predominant with a strenuous expression in advanced age as it mainly implies the detrusor which is less dependent on estrogens.

## CONCLUSION

In our community-dwelling population of menopausal females urinary incontinence remains the main motive for urodynamics and there is an increasing complaint of urgency with ageing. The lack

of adaptation of the sphincter to bladder filling could explain the complaint of incontinence. The role of ageing clearly results from deterioration in bladder function leading to DO, DHIC and DUA in the oldest group. Due to the brisk changes in detrusor function between the middle and the oldest age groups the role of ageing appears to predominate. Further studies are needed to search for a better understanding of the neural control of micturition in ageing women and to better define the conditions leading to impaired detrusor function in the oldest age groups.

### CONFLICT OF INTEREST

None declared.

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# Laparoscopic Skill Laboratory in Urological Surgery: Tools and Methods for Resident Training

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## ABSTRACT

*Purpose:* Laparoscopy has certainly brought considerable benefits to patients, but laparoscopic surgery requires a set of skills different from open surgery, and learning in the operating room may increase surgical time, and even may be harmful to patients. Several training programs have been developed to decrease these potential prejudices.

*Purposes:* to describe the laparoscopic training program for urological residents of the “Hospital das Clinicas” of the Sao Paulo Medical School, to report urological procedures that are feasible in dry and wet labs, and to perform a critical analysis of the cost-benefit relation of advanced laparoscopic skills laboratory.

*Materials and Methods:* The laparoscopic skill lab has two virtual simulators, three manual simulators, and four laparoscopic sets for study with a porcine model. The urology residents during their first year attend classes in the virtual and manual simulator and helps the senior urological resident in activities carried out with the laparoscopic sets. During the second year, the urological resident has six periods per week, each period lasting four hours, to perform laparoscopic procedures with a porcine model.

*Results:* In a training program of ten weeks, one urological resident performs an average of 120 urological procedures. The most common procedures are total nephrectomy (30%), bladder suture (30%), partial nephrectomy (10%), pyeloplasty (10%), ureteral replacement or transuretero anastomosis (10%), and others like adrenalectomy, prostatectomy, and retroperitoneoscopy. These procedures are much quicker and caused less morbidity.

*Conclusion:* Laparoscopic skills laboratory is a good method for achieving technical ability.

**Key words:** *laparoscopy; urology; surgery; training; internship and residency*

**Int Braz J Urol. 2011; 37: 108-12**

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## INTRODUCTION

Today, there is no doubt that minimally invasive surgery is the method of choice by patients and surgeons as an approach to most urological surgical pathologies. It has brought considerable benefits to patients such as, smaller incision with better cosmetic results, reduced morbidity, faster recovery, and shorter hospital length of stay (1). Laparoscopic procedures are certainly the most important technique that fulfills these purposes. However, laparoscopic surgery re-

quires a different set of skills from open surgery, and learning in the operating room may increase surgical time and even morbidity for patients, moreover, it may be against ethical principles.

The acquisition of basic laparoscopic skills may help beginners who are learning laparoscopic procedures. However, it demands considerable time and dedication from trainees and also requires appropriate teaching facilities. Current training involves the use of box trainers, virtual reality, and animal models. Box trainers with either innate models or animal tis-

sues lack objective assessment of skill acquisition. Virtual reality simulators have the ability to teach laparoscopic psychomotor skills, and objective assessment is now possible using dexterity-based and video analyses systems (2).

A recent survey (3) of surgery residency program directors revealed that 55% of surgery training programs have used laparoscopic skills laboratories. Nowadays, a resident in surgery is not allowed to end his/her training program without being able to perform laparoscopic surgery. Numerous protocols for laparoscopic skills training using virtual simulators and animal models have been described in the literature. However, there is a lack of guidelines about the training of an urologist for improving such skills.

The aims of this study were: to describe the laparoscopic training program of the urological residents of the “Hospital das Clinicas” of the Sao Paulo Medical School, University of Sao Paulo, to report urological procedures that are feasible in manual and virtual simulators and with porcine model, and to perform a critical analysis of the cost-benefit relation of advanced laparoscopic skill laboratories.

## MATERIALS AND METHODS

The laparoscopic skill laboratory of the “Hospital das Clinicas” of the Sao Paulo Medical School, University of Sao Paulo, has completed three years in the training of urological residents. The urology department has 15 residents (five residents are admitted per year for a three years course). It has two virtual and three manual simulators and four laparoscopic sets for studying with a porcine model (Figure-1). The materials (laparoscopic equipments and threads) are acquired from donations or are bought at low-cost from retail stores. The animals are donated by a private group. A salaried laboratory manager is responsible for maintaining the laboratory schedule, setting-up, and keeping records of laboratories expenditures. It is estimated that the total direct or indirect expenses funded both by the Government or private sources amount about US\$ 1.0 M in the project and construction of this advanced laparoscopic skill laboratory.

The urological resident, during his first year, attends classes in the virtual and manual simulator

once a week (basic skills) and helps the senior urological residents twice a week in activities with the laparoscopic sets. During the second year, the urological resident has six periods per week, each period lasting four hours, for performing laparoscopic procedures with a porcine model. These procedures range from nephrectomy, simple bladder suture or transureteroanastomosis, pyeloplasty, and prostatectomy. Six pigs are available per week and all activities are supervised by one staff surgeon of the laparoscopic group of the urology department. Once a week, this resident also performs one laparoscopic surgery on a patient in the operating room of our service, always in the presence of a physician supervisor. The period for training each resident in our service lasts for ten weeks.

## RESULTS

By the end of the ten week training program one urological resident has carried out an average of 120 urological procedures. The most common procedures are total nephrectomy (30%), bladder suture (30%), partial nephrectomy (10%), pyeloplasty (10%), ureteral replacement or transureteroanastomosis (10%) and others like adrenalectomy, prostatectomy, and retroperitoneoscopy. All procedures follow the stages of surgery done on human beings with a great similarity.



*Figure 1 – View of the laparoscopy unit.*

The first year urology resident also improves their skills. After helping the senior resident for ten weeks, they are familiarized with abdominal access and proper trocar placement, is completely adapted to laparoscopic bi-dimensional vision, and is capable of performing basic tasks such as sutures, points and even more complex procedures such as total nephrectomies.

The benefits are evident in the real operating room. The residents become more familiarized with the procedures, the mean time of procedures decreases and fewer complications are observed in the last weeks of the training program. The results are procedures that are quicker, safer, and with less morbidity. It also represents an economy, since less time is spent in the operating room and patients are released earlier.

## COMMENTS

Minimally invasive techniques as laparoscopy are more and more responsible for higher proportion of total surgical procedures performed in operating rooms. Issues such as quality control and patient safety, combined with increasing financial constraints and cost-effective results in operating rooms have to be considered as a need for more skills training laboratories (4). Computer-based virtual reality systems have recently been developed and incorporated into some surgery residents training programs (5-9). A recent survey done in USA revealed that 85% of general surgery program directors consider skills labs effective for improving operating room performance, however, only 55% have skills labs. Ninety-nine percent of these have video trainer equipment and 46% have virtual reality trainer equipment. On average, residents train for 0.8 hours per week (range 0 to 6), and this training is mandatory for 55% and supervised for 73%. The mean development cost was US\$ 133,000 (3). This period of training is shorter than the one proposed in our laparoscopic skill lab, where one resident spent more than 20 hours per week for a period of ten weeks.

Surgical skills laboratories provide residents with the opportunity to acquire technical skills in a low stressed and stimulated environment, while focusing on learning and repeating key stages of procedures in

a setting where they are able to reduce their learning curve with the goal of decreasing potential harm to patients (10).

Some authors have reported the benefits of laparoscopic training program. Vlaovic et al. (11) reported their experience with 101 urologists submitted to a one-week laparoscopic training program and concluded that it significantly improved laparoscopic skills. Pareek et al. (12) reported the results of a 2-day course of laparoscopic training. Of the participants that answered the survey, 97% reported that their laparoscopic practice had expanded after taking course. Condous et al. (13) in a prospective observational study with 24 surgeons concluded that laparoscopic skills workshops could improve both knowledge and motor skill.

Several studies have tried to compare the tools now available for training and development of laparoscopic skills. Manda et al. (14) compared the combination of virtual reality and box training. Twenty-four students were grouped according to four training methods: virtual reality training, inanimate box training, a combination of both and no training. Post hoc analyses showed statistically significant differences between the participants with both trainers and control subjects. Combination of virtual reality training and inanimate box training leads to a better laparoscopic skill acquisition than either training method alone or no training at all. Munz et al. (4) compared the virtual reality simulator with the classical box trainer. Again twenty-four beginners were divided into three groups: virtual reality simulator, box trainer and no training and the authors found that both trained groups made significant improvements in all parameters measured, however there was no difference between the tools of training. They concluded that they are equally effective in teaching psychomotor skills, but a large cohort may show different results. We were not able to compare the development of our residents, since the training was basically performed in laparoscopic sets, where objective evaluation is very limited. Our impression is that the benefits are real with a great increase in laparoscopic skills of our residents who become more prepared for surgery in the operating room. Moreover, porcine models made it possible to perform a larger number of urological procedures. Perhaps in a future

study we may be able to compare mean surgical time, blood loss, and other parameters before, during, and after our training program, in surgeries performed in the lab and in the real operating room.

The studies available today are very limited as far as cost analysis is concerned. Berg et al. (10) reported that they are able to provide surgical skills training for about \$1,000 per resident per year; however the costs of donated services, equipment, and supplies were not estimated. We have a similar problem in our cost assessment, because our material was acquired from donations or was bought at low-cost from retail stores.

## CONCLUSION

Laparoscopic skills laboratory are an effective way for achieving technical skills in an optimal environment and with the potential of being less harmful to patients.

## CONFLICT OF INTEREST

None declared.

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**EDITORIAL COMMENT**

Authors present their experience with a resident laparoscopic skill laboratory and a formal training program for urology residents. It is our belief as well that these programs should be present in all urology residency programs. There is no discussion about the important and definitive role of laparoscopic surgery, and formal training programs are essential. Several randomized studies have evaluated the role of these training programs (1), and they help to make surgical procedures faster and more precise. Additional measures, as preoperative warm-up also seems to be of value (2). Expensive virtual reality simulators are interesting, but far from being necessary. The Hospital das Clinicas' center is interesting, and an honored model. We believe that similar but cheaper models are possible and as effective as expensive centers, and are important to make these structures accessible throughout Brazil. A progressive approach to simulation with increasing complexity and a well-designed training curriculum is definitively the best model. We have adopted the initial step of the curriculum of our residents-in-training at a dry lab, through exercises that can be objectively evaluated (time and perfection

to perform each exercise). The second step is to performed specific surgical procedures, such as ureteral, intestinal, urethro-vesical anastomoses, pyeloplasty, nephrectomy, etc., either in the dry lab or in porcine models. It is important to mention however, that animal training should be reduced to the minimum necessary, for ethical reasons; and the third step is to observe, participate and perform real surgical procedures. Additionally, these training models can also help to maintain skills for surgeons already in practice.

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## Emphysematous Cystitis as Complication in Chronic Rejection of Renal Transplant

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This 43-year-old Caucasian female presented in a septic condition in the emergency room. At the time of admission her temperature was 38.5 Celsius, white blood cells (WBC) 12800, red blood cells 3.8 mill, hemoglobin 10.8, hematocrit 36, urea 28 mg/dl, serum creatinine 3.2 mg/dl, K 5.8 meq/l, Na 128 meq/l, alk pta 142 U/l. Urine analysis 50 WBC/hpf, innumerable bacteria/hpf, cellular debris, gas bubbles. Both urine and later blood cultures revealed *E. coli*.

The lower abdomen and pelvis were exquisitely tender to palpation. Patient had been hemodialyzed 2 days earlier. Patient had received a cadaver-transplant 3 years ago, which functioned well until 4 months ago. At this time chronic rejection was diagnosed. An antegrade pyelogram revealed a stricture at the implant site of the cadaver ureter, dilatation and possible ulcerations of the mid – and upper ureter. Bullous edema of the native bladder was seen, most prominent near the implant site. Immunosuppressive therapy was instituted and despite these efforts, function of the transplant kidney continued to deteriorate and the patient was finally put on hemodialysis 1 month ago. It was contemplated to perform a uretero-neo-calicostomy with the still present native ureter to hopefully salvage the kidney

A non-contrast multi-detector computed tomography demonstrated gas in the submucosa and bladder, and also extravascular anterior to the bladder (Figure-1). Strands of debris and sloughed tissue surrounded by air are seen in the bladder lumen (arrow). Gas has dissected along the anterior abdominal wall

(Figure-2). A coronal reconstruction shows relatively little striation in the perirenal space. There is edema in the peripelvic area and around the upper ureter (Figure-3).

To control the fulminating gas forming infection, bladder, transplant kidney and ureter were removed, the space of Retzius drained. Depending on the severity of the infection and underlying conditions such as diabetes mere control of the diabetes and appropriate antibiotic therapy may suffice while severe forms may mandate surgical intervention to remove the necrotic debris (1-3). After prolonged antibiotic



**Figure 1** – A non-enhanced axial CT of the pelvis demonstrates gas in the submucosa and bladder lumen. Necrotic material and debris are outlined by gas in the bladder. An ileal loop is adherent to and indenting the bladder. Some extraluminal gas is dissecting toward the anterior abdominal wall.



**Figure 2** – Gas is dissecting anteriorly into the space of Retzius and laterally toward the abdominal wall and inguinal fossa. Note tissue debris outlined by gas in the bladder and a soft tissue mass (ileal loop) indenting the bladder.

therapy and hemodialysis the patient recovered and received a second successful transplant kidney.

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**Figure 3** – A coronal reconstruction shows debris and an adherent ileal loop outlined by the gas-filled bladder. A transplant kidney is seen on the left side, with only minimal stranding in the perirenal space. However edema is seen peripelvic and peri-ureteral space.

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## UROLOGICAL SURVEY

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## STONE DISEASE

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**The effect of fat and nonfat components of the skin-to-stone distance on shockwave lithotripsy outcome**

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J Endourol. 2010; 24: 1825-9

Background: Few studies have addressed the effect of skin-to-stone distance (SSD) on the success of extracorporeal shockwave lithotripsy (SWL). Nevertheless, the effect of the two components of SSD, that is, the fat SSD (FSSD) and nonfat SSD (NFSSD) components, was not previously investigated.

Methods: In this prospective study, all patients (n = 113) who had single radio-opaque kidney stones and underwent SWL for the first time between January 2006 and June 2007 were recruited. SSD, FSSD, and NFSSD were measured by noncontrast CT scan at 0°, 45°, and 90° and the average was calculated. The outcome was defined as successful (completely stone free or residual fragments ≤ 3 mm) or unsuccessful (residual fragments > 3 mm or complete failure of fragmentation).

Results: Sixty-nine (61%) patients had successful treatment. On univariate analysis, SSD, FSSD, and NFSSD were significantly lower in the successful group compared with those with unsuccessful outcome (71.9 ± 13.3 vs. 86.2 ± 25.1 mm [p = 0.001], 27.2 ± 10.3 vs. 36.1 ± 17.3 mm [p = 0.011], and 44.7 ± 7.2 vs. 50.1 ± 13.9 mm [p = 0.02], respectively). The muscle component of the NFSSD was also lower in the successful group (21.5 ± 4.1 vs. 25.2 ± 10.0 mm [p = 0.01]). On multivariate analysis, factors that independently predicted treatment success were SSD, stone attenuation, and stone size but not the FSSD or NFSSD.

Conclusions: Although the total SSD appeared to be a significant predictor of SWL success, its fat and nonfat components did not independently predict the final outcome and only appeared to be important through their contribution to the total SSD.

**Editorial Comment**

It is important to note that the average skin-to-stone distance (SSD) of 7.8 cm and average BMI of 25 indicates that the study population was relatively healthy, and it may be worthwhile to extend this study to patients with morbid obesity to confirm that the relative contribution of fat vs. muscle to the SSD does not affect efficacy. The article has important implications. Despite the fact that disproportionate amounts of fat vs. non-fat in the retroperitoneum have been reported in child vs. adult, athlete vs. obese, Asian vs. Caucasian; for ESWL, differences in skin-to-stone distance are more important than the type of tissue between the shock and the stone; specifically the main issue is the distance traveled. The other major contribution of this article relates to their stringent evaluation of success with CT scans at 6 weeks and well defined endpoints. Specifically, with a mean stone size of about 12 mm, approximately 40% were stone-free, 20% had residual fragments < 3 mm, 30% had residual fragments > 3 mm and 10% had no fragmentation. It is feasible that as 92% of patients were treated with sedation, higher success rates might have been noted with general anesthesia as reported in other studies.

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**Emergency ureteroscopic treatment for upper urinary tract calculi obstruction associated with acute renal failure: feasible or not?**

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J Endourol. 2010; 24: 1721-4

**Purpose:** To determine the efficacy and safety of emergency ureteroscopy (URS) and holmium:yttrium-aluminum-garnet (Ho:YAG) laser lithotripsy for ureteral calculi that are associated with acute renal failure (ARF).

**Patients and Methods:** We retrospectively evaluated a cohort of 49 patients who underwent URS from November 2005 to November 2008 for ARF that was caused by calculi obstruction of the upper urinary tract. The mean (maximal diameter) stone size was 1.48 cm. Acute renal failure was demonstrated by oliguria or anuria and marked increase in serum creatinine and blood urea nitrogen levels. All the patients were treated with URS and Ho:YAG laser lithotripsy emergently. Ureteral stent placement was performed in all cases after lithotripsy. A plain film of the kidneys, ureters, and bladder and abdominal ultrasonography were performed to evaluate efficacy of treatment on the first day postoperatively. Serum creatinine and blood urea nitrogen levels and urine volume were successively monitored until they returned to normal. All patients had postoperative imaging, including ultrasonography and excretory urography, to confirm stone clearance and exclude late obstructive complications 3 months after URS.

**Results:** URS and laser lithotripsy were successfully performed in all patients. There were no major intraoperative complications, and no procedure was converted to open surgery. The mean operative time was 35 minutes. The successful fragmentation rate was 95.5%. The overall stone-free rate was 91.8%. Normal renal function returned in 46 (93.8%) patients within 7 days. No postoperative ureteral stricture occurred after 3 months.

**Conclusions:** URS and Ho:YAG laser lithotripsy represent an effective and safe modality for treating patients with ARF that is caused by calculi obstruction of the upper urinary tract in strictly selected situations.

**Editorial Comment**

The authors report remarkable results (92% stone-free rates, ability to reach all proximal ureteral stones) despite using a relatively large semi-rigid ureteroscope and not utilizing a flexible ureteroscope for any cases. Indeed, they report treating stones larger than 3 cm in size in less than 1 hour. They utilized higher energy settings (1.8 J), which may facilitate more rapid fragmentation, but have been reported in "in vitro" studies to lead to larger stone fragments. It may be that the longer stenting times (4-12 weeks) helped facilitate stone passage without the development of recurrent obstruction. The authors provide important information concerning the safety of ureteroscopy in the face of acute renal failure, and the course of resolution of the renal failure with alleviation of the obstruction. Likely, the short operative time is critical in these patients to minimize the risks of peri-operative complication related to irrigant fluid absorption and length of anesthetic.

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**Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer**

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J Urol. 2010; 183: 1822-8

**Purpose:** Health related quality of life concerns factor prominently in prostate cancer management. We describe health related quality of life impact and recovery profiles of 4 commonly used operative treatments for localized prostate cancer.

**Materials and Methods:** Beginning in February 2000 all patients treated with open radical prostatectomy, robot assisted laparoscopic prostatectomy, brachytherapy or cryotherapy were asked to complete the UCLA-PCI questionnaire before treatment, and at 3, 6, 12, 18, 24, 30 and 36 months after treatment. Outcomes were compared across treatment types with statistical analysis using univariate and multivariate models.

**Results:** A total of 785 patients treated between February 2000 and December 2008 were included in the analysis with a mean followup of 24 months. All health related quality of life domains were adversely affected by all treatments and recovery profiles varied significantly by treatment type. Overall urinary function and bother outcomes scored significantly higher after brachytherapy and cryotherapy compared to open radical prostatectomy and robotic assisted laparoscopic radical prostatectomy. Brachytherapy and cryotherapy had a 3-fold higher rate of return to baseline urinary function compared to open radical prostatectomy and robotic assisted laparoscopic radical prostatectomy. Sexual function and bother scores were highest after brachytherapy, with a 5-fold higher rate of return to baseline function compared to cryotherapy, open radical prostatectomy and robotic assisted laparoscopic radical prostatectomy. All 4 treatments were associated with relatively transient and less pronounced impact on bowel function and bother.

**Conclusions:** In a study of sequential health related quality of life assessments brachytherapy and cryotherapy were associated with higher urinary function and bother scores compared to open radical prostatectomy and da Vinci prostatectomy. Brachytherapy was associated with higher sexual function and bother scores compared to open radical prostatectomy, robotic assisted laparoscopic radical prostatectomy and cryotherapy.

**Editorial Comment**

The authors compared 4 commonly used operative treatments for localized prostate cancer: open radical prostatectomy (ORP), robot assisted laparoscopic prostatectomy (RALP), brachytherapy (BT) or cryotherapy.

A total of 785 patients were included in the analysis with a mean follow-up of 24 months.

BT and cryotherapy were associated with a 3-fold higher rate of return to baseline urinary function compared to ORP and RALP. Moreover, all treatments had a more adverse impact on sexual function and bother than on urinary and bowel domains.

Although the advent of RALP has improved visualization and surgeons' ergonomics it has not demonstrated a significant improvement of urinary continence or sexual function in this prospective, longitudinal study of health-related quality of life outcomes using validated self-reported questionnaires.

The authors have shown the 8 years clinical follow-up analyzing different treatment modalities for localized prostate cancer. I believe this assessment should be followed by health care providers managing patients with prostate cancer so we can better serve our patients.

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## IMAGING

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### **Positive predictive value of CT urography in the evaluation of upper tract urothelial cancer**

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AJR Am J Roentgenol. 2010; 195: W337-43

**Objective:** The purpose of this study was to determine the positive predictive value of CT urography in the diagnosis of upper tract urothelial malignancies.

**Materials and Methods:** Retrospective review of the records of patients who underwent 2,602 CT urographic examinations revealed that 81 (3%) examinations of 77 patients had findings suggesting upper tract urothelial cancer. Two radiologists in consensus categorized the findings as large masses (> 5 mm), small masses ( $\leq$  5 mm), or urothelial thickening. The positive predictive value of CT urography was determined with the findings at pathologic examination (n = 42), followup imaging (n = 29), or clinical follow-up alone (n = 5). One patient with insufficient follow-up information was excluded. The effects of age, sex, indication for examination, imaging appearance, and urine cytology were analyzed with the Fisher's exact test or Student's t test. Multivariate logistic regression analysis was used to generate a model for predicting the probability of the presence of upper tract urothelial cancer in patients with positive CT urographic examinations.

**Results:** The positive predictive value of CT urography for upper tract urothelial cancer was 53% (40/76) overall, 83% (29/35) for large masses, 0% (0/17) for small masses, and 46% (11/24) for urothelial thickening. Imaging appearance, urine cytology, and age were significant univariate predictors ( $p < 0.05$ ) of the presence of upper tract urothelial cancer in patients with positive CT urographic examinations. The independent variables most likely associated with upper tract urothelial cancer were urine cytology (odds ratio, 60.0; 95% CI, 5.5-653.7) and imaging appearance (odds ratio, 24.4; 95% CI, 3.0-201.9) after adjusting for age and clinical indication.

**Conclusion:** The positive predictive value of CT urography for upper tract urothelial cancer is moderate because benign findings mimic cancer. Positive findings on a CT urogram are more likely to indicate cancer in the setting of large masses or positive urine cytology.

### **Editorial Comment**

Several studies have been shown that multidetector computerized tomography urography (CT urography) is more sensitive, specific and accurate than excretory urography in the diagnosis of upper urinary tract

transitional cell carcinoma in patients with hematuria and in patients with history of urothelial cancer. In this retrospective study the authors shows that positive predictive value (PPV) of abnormal findings suspicious for upper tract urothelial cancer on CT urography was only moderate, that is 53% (of 76 patients with either minimally or highly suspicious findings, only 40 had pathologically proved upper tract urothelial cancer). CT urography findings suspicious for urothelial carcinoma were classified in three main categories: large mass (lesions > 5 mm in maximum diameter), small mass (lesions 5 mm in maximum diameter), or urothelial thickening. For findings classified as large masses, the PPV was 83% and for small masses was 0%. We have to consider however, the large number and the variety of false-positive findings in this study. This was probably related to the retrospective analysis of reported findings. False positive findings were caused mainly by normal or hypertrophied papilla, blood clot and inflammation. Usually nonenhancing blood clots may be differentiated from enhancing urothelial tumor by comparing the findings between non-contrast phase and nephrographic phase. Presence of mild, homogeneously enhanced and thickened pelvicalyceal urothelium is relatively frequent feature of patients with symptomatic or asymptotically urinary tract infection. Normal prominent renal papillae may occasionally invaginate deeply into the calices and thus simulate urothelial tumor. The awareness of such anatomic variation and the search for this finding in other papillae in the same patient, are helpful for the adequate diagnosis.

The authors of this manuscript, however, offered important information regarding the value of urine cytology studies, which were available in 80% of patients. Urine cytology was very important for the adequate characterization of pelvicalyceal abnormalities, such as urothelial tumor. When urine cytology was suspicious or malignant and an upper tract urothelial abnormality was found at CT urography, the PPV for upper tract urothelial carcinoma was 92%.

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### **Urinary calculi composed of uric acid, cystine, and mineral salts: differentiation with dual-energy CT at a radiation dose comparable to that of intravenous pyelography**

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Radiology. 2010; 257: 402-9

**Purpose:** To retrospectively evaluate radiation dose, image quality, and the ability to differentiate urinary calculi of differing compositions by using low-dose dual-energy computed tomography (CT).

**Materials and Methods:** The institutional review board approved this retrospective study; informed consent was waived. A low-dose dual-energy CT protocol (tube voltage and reference effective tube current-time product, 140 kV and 23 mAs and 80 kV and 105 mAs; collimation, 64 × 0.6 mm; pitch, 0.7) for the detection of urinary calculi was implemented into routine clinical care. All patients (n = 112) who were examined with this protocol from July 2008 to August 2009 were included. The composition of urinary calculi was assessed by using

commercially available postprocessing software and was compared with results of the reference standard (ex vivo infrared spectroscopy) in 40 patients for whom the reference standard was available. Effective doses were calculated. Image quality was rated subjectively and objectively and was correlated with patient size expressed as body cross-sectional area at the level of acquisition by using Spearman correlation coefficients.

Results: One calcified concrement in the distal ureter of an obese patient was mistakenly interpreted as mixed calcified and uric acid. One struvite calculus was falsely interpreted as cystine. All other uric acid, cystine, and calcium-containing calculi were correctly identified by using dual-energy CT. The mean radiation dose was 2.7 mSv. The average image quality was rated as acceptable, with a decrease in image quality in larger patients.

Conclusion: Low-dose unenhanced dual-source dual-energy CT can help differentiate between calcified, uric acid, and cystine calculi at a radiation dose comparable to that of conventional intravenous pyelography. Because of decreased image quality in obese patients, only nonobese patients should be examined with this protocol.

### Editorial Comment

Nowadays multi-detector computed tomography (MDCT) is used in attempt to determine the chemical composition of urinary tract stones. However, the attenuations values given in Hounsfield units of different types of calculi obtained with current technique overlap, making reliable distinction of chemical composition of urinary calculi very difficult. With the advent of new dual-source CT systems, CT scans are simultaneously and quickly obtained using two orthogonally positioned x-ray tubes and detector sets (double source at 80 and 140 kV); both helical acquisitions run simultaneously and are not limited by changes between the two scans in contrast enhancement or patient motion (1). Dual-energy CT may be used to distinguish pure uric acid, mixed uric acid, and calcified stones. However, dual-source CT imaging delivery a higher radiation dose to the patient than the currently recommended lower-dose MDCT protocols.

The authors of this manuscript offer a great contribution to this subject by developing a low-dose unenhanced dual-source dual-energy CT protocol that can help differentiate between calcified, uric acid, and cystine calculi at a radiation dose comparable to that of conventional intravenous pyelography (mean 2.7 mSv). This protocol however was useful only in nonobese patients. New variation in dual-source CT protocols, are still in progress in an attempt to further decrease the radiation dose to the patients while keeping the ability to differentiate chemical composition of urinary tract calculi (1).

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## PATHOLOGY

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**Application of the Epstein criteria for prediction of clinically insignificant prostate cancer in Korean men**

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BJU Int. 2010; 105: 1526-30

**Objective:** To investigate the rate of pathologically confirmed unfavourable prostate cancers among Korean men who fulfilled the contemporary Epstein criteria for clinically insignificant prostate cancer.

**Patients and Methods:** This was a retrospective study of 131 Korean men who underwent radical prostatectomy (RP) for clinically insignificant prostate cancer as defined by contemporary Epstein criteria. We assessed the percentage of unfavourable prostate cancer (pathological Gleason sum  $\geq 7$  and/or extraprostatic extension [EPE]) among these men and tried to identify useful predictors for such unfavourable tumour profiles using uni- and multivariate analyses.

**Results:** Among 131 men with clinically insignificant prostate cancer, 40 (30.5%) had pathological Gleason  $\geq 7$  tumours after RP. Of these 40 men, four (3.1%) also had EPE on examination of RP specimen. All those who did not have Gleason score upgrading after RP had organ-confined disease from examination of RP specimen. Overall, 40 (30.5%) of the 131 men who fulfilled the contemporary Epstein criteria for clinically insignificant prostate cancer before RP had pathologically unfavourable disease. Among our patients, no significant preoperative predictor of pathologically unfavourable disease was identified using uni- and multivariate analyses.

**Conclusion:** Our results showed that a significant proportion of contemporary Korean patients who meet all the conditions of the contemporary Epstein criteria for prediction of clinically insignificant prostate cancer might actually harbour prostate cancer with unfavourable pathological features. Such findings should be considered when treatment options are contemplated based upon the Epstein criteria among Asian patients.

**Editorial Comment**

Watchful waiting (active surveillance) has gaining popularity as a management strategy for newly diagnosed low-grade, limited cancer on needle biopsy based on the large discrepancy between incidence and mortality rate of prostate cancer. Data from the European Randomized Study of Screening for Prostate Cancer Trial showed that PSA screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis (1).

Epstein proposed a set of criteria based on PSA and preoperative biopsy features that identify a high likelihood of organ-confined insignificant cancers at radical prostatectomy (2). Insignificant cancers are defined as cancers confined to the prostate (pT2), Gleason low-grade (score  $\leq 6$ ), and low-volume ( $\leq 0.5$  cc). It is important to be aware that insignificant cancer is not synonymous of latent (indolent) carcinoma. So far, there is no single marker of biological behavior for prostate cancer.

The preoperative biopsy and clinical features of Epstein's criteria for insignificant cancer are: clinical stage T1c, preoperative PSA density  $< 0.15$ , no Gleason pattern 4 or 5, no more than 2 cores with cancer, and no more than 50% of involvement of cancer in a single core. According to Bastian at Johns Hopkins, the predictive value using the Epstein's criteria for organ-confined disease and insignificant cancer is 92% and 84%, respectively.

Several studies have applied Epstein's criteria for prediction of clinically insignificant prostate cancer with differing results. In all studies, the criteria are predictive of a high frequency of organ-confined disease

but differ for insignificant cancer. In the study from Korea, the frequency of organ-confined disease was 97% (vs. 92% from Johns Hopkins) but 69% for insignificant cancer (vs. 84% from Johns Hopkins).

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## **The Epstein criteria predict for organ-confined but not insignificant disease and a high likelihood of cure at radical prostatectomy**

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*Eur Urol.* 2010; 58: 90-5

Background: Few reports attempt to validate the role of Epstein criteria in selecting patients for an active surveillance protocol.

Objective: To determine the performance of the Epstein biopsy criteria for predicting pathologic end points and biochemical relapse-free survival (bRFS) in men with early stage prostate cancer (PCa) treated by radical prostatectomy (RP).

Design, Setting and Participants: Between October 1999 and January 2007, 746 consecutive patients were biopsied, and then underwent RP at our tertiary care institution. Two hundred sixty-eight patients met the entry criteria of Gleason 6 disease only on initial biopsy with complete pathologic information.

Measurements: Primary end point was insignificant disease. Insignificant disease was defined using a classical (organ-confined, Gleason score < 6, and tumor volume < 0.5 cm<sup>3</sup>) and more liberal (organ-confined, Gleason < 6 tumor of any volume) formulation. Secondary end points included organ-confined disease and bRFS.

Results and Limitations: One hundred thirty-six men (51%) met the Epstein biopsy criteria, and 167 (62%) had organ-confined cancer. Insignificant disease by the classical and liberal definitions was present in 68 (25%) and 92 (34%) patients, respectively. Cases meeting Epstein biopsy criteria were more likely to have insignificant disease by either definition ( $p < 0.001$ ) and more likely to have organ-confined tumors ( $p < 0.001$ ). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) varied widely among the end points, with sensitivity (74%) and NPV (86%) best for the classical definition of insignificant disease and specificity (74%) and PPV (92%) best for organ-confined disease. The estimated 5-yr bRFS was 100% for those meeting Epstein biopsy criteria compared to 83% for those not meeting these criteria.

Conclusions: The Epstein biopsy criteria predict for a high likelihood of organ-confined disease and the absence of biochemical failure up to 5 years after RP. These criteria are insufficiently robust to predict the presence of biologically insignificant disease.

### Editorial Comment

The conclusion of Lee's et al. study from Cleveland Clinic is that Epstein biopsy criteria predict for a high likelihood of organ-confined disease but are insufficiently robust to predict the presence of insignificant disease defined as organ-confined, Gleason low-grade, and minimal volume ( $\leq 0.5$  cc).

The findings are supported by other studies (1-3). Epstein's criteria are highly predictive for organ-confined prostate cancer. The frequency varies from 91% to 97%. However, the predictive value for insignificant cancer varies from 37% to 84%. Jeldre's et al. concluded that Epstein's criteria might underestimate the true nature of prostate cancer in as many as 24% of European patients (1). Approximately 31% Korean patients who meet all the conditions of the contemporary Epstein's criteria for prediction of clinically insignificant prostate cancer may actually harbor prostate cancer with unfavorable pathological features (2). In the Middle East (Egypt), 46% of patients may present unfavorable cancer (3).

There are several causes for the discrepancies. Prostate cancers diagnosed in Asian, American, and European men may have innate differences associated with racial and/or environmental factors. However, methodological factors seem to be more important: among others, number of patients studied, number of cores of the biopsy, and criteria for volume evaluation. The last one was considered by Lee's et al. study from the Cleveland Clinic.

According to volume, the authors defined prostate cancer by two ways: classical and liberal. The classical definition considered a tumor volume  $< 0.5$  cc; and the liberal definition any grade of volume. Using the liberal definition, the predictive value of Epstein's criteria for insignificant cancer was 58%; using the classical definition was 37%. In a similar study at our Institution (data not published), the frequency was 55% and 46%, respectively.

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## RECONSTRUCTIVE UROLOGY

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### **The use of penile skin graft versus penile skin flap in the repair of long bulbo-penile urethral stricture: a prospective randomized study**

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*Urology.* 2011 Jan 3. [Epub ahead of print]

**Objectives:** To evaluate the use of penile circular skin graft versus flap as a ventral onlay for bulbo-penile stricture urethra.

**Material and Methods:** Between 2003 and 2009, 37 patients with bulbo-penile stricture were randomized to penile methods circular skin graft (PCG = 18) or flap (PCF = 19). Inclusion criteria included postinstrumentation or idiopathic stricture. Exclusion criteria were unhealthy skin and previous urethrotomy/urethroplasty. Patients had urethrogram at three weeks, three months, one year, and urethroscopy when needed. Any subsequent urethrotomy/urethroplasty was considered a failure. Chi-square and Student's t test were used for analysis.

**Results:** Patients' ages were 45.3 (range: 30-65) and 45.5 (35-60) yr in PCG&PCF respectively. Stricture length was 15.2 (10-22) & 14.1 (9-21) cm in PCG&PCF respectively. The stricture was postinstrumentation in 9 and 11 and idiopathic in 9 and 8 patients in PCG&PCF respectively. Mean follow up was 36.2 (12-60) and 37.1 (range: 13-24) months in PCG and PCF respectively. Operative time was significantly shorter in PCG than in PCF (203.3 and 281.6 min, respectively;  $P = .000$ ). Early postoperative complications were similar in both groups. Superficial skin necrosis occurred only in the PCF group (3 cases). Late complications of mild postvoid dribbling occurred similarly in both groups. One patient in PCF had a urethro-cutaneous fistula at the level of fossa navicularis that was repaired later. Stricture recurred in 5 (27.7%) and 4(21%) patients in PCG and PCF, respectively ( $P = .249$ ). Four patients had visual internal urethrotomy (2, 2), four needed anastomotic urethroplasty (2, 2) in PCG and PCF, respectively, and one needed buccal mucosal graft in the PCG group.

**Conclusions:** At intermediate follow-up, both penile circular graft and flap had similar and high success as a ventral onlay for repair of long bulbo-penile stricture with a low rate of complications.

### Editorial Comment

Hussein et al. raise the bar in reconstructive urology research by completing a randomized clinical trial of distal penile fasciocutaneous skin flap urethroplasty vs. distal penile skin graft urethroplasty for non- lichen sclerosus strictures of the bulbo-penile urethra. They chose to compare two surgical techniques, which were similar in many ways but distinct in one important way. Similarities included the circumcising incision, the distal penile skin and the ventral onlay approach. The difference was in whether a graft or flap was used. The similarities in technique were likely helpful in recruiting patients. The similarities were also important in helping isolate the treatment effect of interest – flap vs. graft. Indeed, they did not detect a difference between the two groups in their primary outcome – a subsequent procedure to treat a stricture recurrence (21% for flap vs. 28% for graft). Here is where some additional planning could have strengthened the study. In order to detect a 10% difference at a significance level of  $p = 0.05$  at a power of 0.8 they would have needed to randomize 353 patients to each arm of the study, rather than 19 patients as done here. Indeed, with only 19 patients in each arm they would have only been able to detect a massive difference between the recurrence rates. Additionally, the primary outcome of interest – need for additional procedures – introduces significant subjectivity into the success rates. A more objective outcome measure would have been preferable. Still, this study represents a great advance for the field of reconstructive urology and hope it will stimulate others to contribute randomized studies to the literature.

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## **Halofuginone-coated urethral catheters prevent periurethral spongiofibrosis in a rat model of urethral injury**

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J Endourol. 2011 Jan 4. [Epub ahead of print]

**Background and Purpose:** Urethral strictures are from periurethral spongiofibrosis that develops as a result of urethral trauma, disease, or iatrogenic injury. The spongy tissue that surrounds the strictured urethra has an altered ratio of collagen, with increased collagen type I relative to type III. We evaluated the ability of a urethral catheter that was coated with halofuginone (HF), a potent type I collagen inhibitor, to prevent spongiofibrosis formation in a rat model.

**Materials and Methods:** HF was coated on silicone catheters and release kinetics were measured. Success of impregnation was evaluated with scanning electron microscopy, serial weights, and drug elution data. Urethral strictures were induced in rats using electrocautery. Half the animals had placement of an HF-coated catheter while the others had uncoated silicone controls. Animals were sacrificed at predetermined time points, and urethral tissue was either processed for staining with Masson trichrome and anti-alpha-1 collagen or digested to determine HF concentration. Serum drug levels were also determined in treated animals. Slides were graded by a pathologist who was blinded to treatment to determine collagen deposition.

**Results:** HF was coated successfully on silicone catheters. Local urethral concentration of HF was tenfold higher than serum concentration in treated rats. Animals with HF-coated catheters had no new type I collagen deposition after urethral injury. Control animals had increased periurethral collagen type I deposition, typical of urethral stricture formation.

**Conclusions:** HF can be coated successfully on silicone catheters. HF successfully inhibits periurethral type I collagen deposition after urethral injury. This may become an important therapy to prevent urethral stricture formation or recurrence after endoscopic therapy.

### **Editorial Comment**

The authors present preliminary work in an animal model of urethral injury in which an extract of a Chinese herb is impregnated onto a urethral catheter to prevent build-up of Type 1 collagen. Urethral stricture is known to be associated with accumulation of Type 1 rather than Type 3 collagen in the corpus spongiosum. Halofuginone has been shown to prevent collagen accumulation in other urologic models; however, this is the first study to deliver the compound locally rather than systemically. Indeed, urethral stricture is an attractive field for such a delivery system, in that a urethral catheter provides convenient delivery device. We look forward to future developments in this area.

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**Do patients benefit from routine follow-up to detect recurrences after radical cystectomy and ileal orthotopic bladder substitution?**

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Eur Urol. 2010; 58: 486-94

**Background:** The need for and intensity of follow-up to detect disease recurrence after radical cystectomy (RC) for transitional cell carcinoma (TCC) remains a matter for debate.

**Objective:** To determine whether diagnosis of asymptomatic recurrence after RC by routine follow-up investigations confers a survival benefit versus symptomatic recurrence.

**Design, Setting, and Participants:** Retrospective analysis of 479 patients with nonmetastatic bladder TCC receiving no neoadjuvant chemotherapy/radiation therapy and prospectively followed with a standardised protocol for a median 4.3 yr (range: 0.3-20.9) after RC at an academic tertiary referral centre.

**Intervention:** RC and extended pelvic lymph node dissection with ileal orthotopic bladder substitution.

**Measurements:** Cancer-specific survival (CSS) and overall survival (OS) probability for asymptomatic and symptomatic recurrent patients were estimated using the Kaplan-Meier method. The effects of age, nerve-sparing surgery, pathologic tumour stage, lymph node status, adjuvant chemotherapy, mode of recurrence diagnosis, and recurrence site on survival were assessed with multivariable Cox regression models.

**Results and Limitations:** Of the 174 of 479 patients (36.3%) with tumour recurrence, 87 were diagnosed by routine follow-up investigations and 87 by symptoms. Routine follow-up mostly detected lung metastases and urethral recurrences, while symptoms were predominantly the result of bone metastases and concomitant pelvic/distant recurrences. Of 24 patients with urethral recurrences, 13 had carcinoma in situ (CIS). Of these, 12 were successfully managed with urethra-sparing treatment, and 6 are still alive with no evidence of disease. Most other recurrent long-term survivors had lung and extrapelvic lymph node metastases. Cumulative 5-yr survival rates of the entire cohort were 69.8% (95% confidence interval [CI], 65.5-74.3%) for CSS and 61.9% (95% CI, 57.4-66.7%) for OS. In multivariable analysis, mode of recurrence diagnosis and site of initial recurrence were the only independent predictors of CSS and OS. Patients with recurrences detected by routine follow-up investigations and with secondary urothelial tumours as site of recurrence had a slightly but significantly higher survival probability.

**Conclusions:** Patients diagnosed with asymptomatic recurrences during our routine follow-up after RC had a slightly higher survival than patients with symptomatic recurrences. Routine follow-up appears particularly effective in early detection of urethral CIS, which can be treated conservatively. In addition, the predominance of lung and extrapelvic lymph node metastases in survivors may justify the use of routine cross-sectional imaging.

**Editorial Comment**

Why do patients need follow-up after cystectomy? This retrospective analysis on 174 patients with cystectomy and orthotopic neobladders shows the evidence behind current recommendations of routine follow-up procedures.

Interestingly, only about 7% of patients had isolated pelvic recurrences whereas about 61% had distant recurrences only. Ten percent of patients had concomitant local and distant recurrences. Roughly, half of patients were detected without symptoms by routine follow-up procedures. Especially urethral recurrences, which are easily detected by cytology/biopsy, had the potential of cure.

Thus, routine follow-up including urethral barbotage cytology and routine x-ray analyses are advocated in patients with orthotopic neobladders.

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### **Multicentric oncologic outcomes of high-intensity focused ultrasound for localized prostate cancer in 803 patients**

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Eur Urol. 2010; 58: 559-66

**Background:** High-intensity focused ultrasound (HIFU) is an emerging treatment for select patients with localized prostate cancer (PCa).

**Objectives:** To report the oncologic outcome of HIFU as a primary care option for localized prostate cancer from a multicenter database.

**Design, Setting, and Participants:** Patients with localized PCa treated with curative intent and presenting at least a 2-yr follow-up from February 1993 were considered in this study. Previously irradiated patients were excluded from this analysis. In case of any residual or recurrent PCa, patients were systematically offered a second session. Kaplan-Meier analysis was performed to determine disease-free survival rates (DFSR).

**Measurements:** Prostate-specific antigen (PSA), clinical stage, and pathologic results were measured pre- and post-HIFU.

**Results and Limitations:** A total of 803 patients from six urologic departments met the inclusion criteria. Stratification according to d'Amico's risk group was low, intermediate, and high in 40.2%, 46.3%, and 13.5% of patients, respectively. Mean follow-up was 42+/-33 mo. Mean PSA nadir was 1.0+/-2.8 ng/ml with 54.3% reaching a nadir of < or =0.3 ng/ml. Control biopsies were negative in 85% of cases. The overall and cancer-specific survival rates at 8 yr were 89% and 99%, respectively. The metastasis-free survival rate at 8 yr was 97%. Initial PSA value and Gleason score value significantly influence the DFSR. The 5- and 7-yr biochemical-free survival rates (Phoenix criteria) were 83-75%, 72-63%, and 68-62% (p=0.03) and the additional treatment-free survival rates were 84-79%, 68-61%, and 52-54% (p<0.001) for low-, intermediate-, and high-risk patients, respectively. PSA nadir was a major predictive factor for HIFU success: negative biopsies, stable PSA, and no additional therapy.

**Conclusions:** Local control and DFSR achieved with HIFU were similar to those expected with conformal external-beam radiation therapy (EBRT). The excellent cancer-specific survival rate is also explained by the possibility to repeat HIFU and use salvage EBRT.

### **Editorial Comment**

High-intensity focused ultrasound (HIFU) is not regarded an established treatment in prostate cancer patients as radical prostatectomy and radiation therapy are. Therefore, reports on the long-term outcomes of

patients treated with HIFU are very interesting and should be analyzed carefully. Here, the authors report on 803 patients treated with HIFU against localized primary prostate cancer. Forty percent, 46% and 14% were of low, intermediate and high-risk group according to Amico, respectively. If only the outcomes of the most recently treated patients is regarded, only 57% had a nadir PSA < 0.3, 19% had a nadir PSA between 0.3 and 1, and 19% had a nadir PSA of > 1. The biochemical-free survival rates of these groups are important for the assessment of the curative efficacy. After 7 years of follow-up roughly 90% of patients with a PSA nadir of < 0.3 remained biochemically recurrence-free, whereas these figures were much lower for patients with a PSA nadir of 0.3-1 (~ 50% recurrence-free) and with a PSA nadir of > 1 (~ 40% recurrence-free).

These and other figures show that the cure rate of patients with localized prostate cancer after HIFU treatment to my opinion is not yet comparable to the outcome after radical prostatectomy or modern radiation therapy.

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## NEUROLOGY & FEMALE UROLOGY

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### **Salvage spiral sling techniques: alternatives to manage disabling recurrent urinary incontinence in females**

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*J Urol. 2010; 184: 2429-33*

**Purpose:** Females with recurrent stress urinary incontinence after anti-incontinence surgery represent a therapeutic challenge. In our experience and that of others standard sling procedures have occasionally failed to correct these problems. We determined the effectiveness of various spiral sling techniques used in these cases to manage pipe stem urethras in which conventional slings had failed.

**Materials And Methods:** Between January 2007 and July 2008 we evaluated 30 female patients with persistent stress urinary incontinence after multiple failed anti-incontinence procedures. Preoperative and postoperative evaluation consisted of history, physical examination, number of pads, Stamey score and quality of life questionnaires.

**Results:** We followed 28 patients a minimum of 15 months (range 15 to 18). Mean patient age was 60 years (range 36 to 84). At presentation patients had undergone a mean of 3.5 prior vaginal procedures (range 1 to 6) and used a mean of 7 pads daily (range 3 to 12). Of the patients 21 received a synthetic spiral sling, 5 received an autologous spiral sling (rectus fascia in 3 and fascia lata in 2) and 3 received a lateral spiral sling. Mean pad use decreased to 0.9 daily (range 0 to 2,  $p < 0.05$ ). Postoperative mean Stamey score decreased from 2.6 to 0.3 ( $p < 0.05$ ). Complications included unilateral vesical perforation in 3 patients with a contralateral lateral spiral sling. The overall success rate was 72%.

Conclusions: Salvage spiral sling techniques are a satisfactory alternative treatment for refractory stress urinary incontinence. When synthetic material cannot be used, autologous tissue can provide similar results. When the bladder is perforated unilaterally, a lateral spiral sling can be used on the contralateral side.

### Editorial Comment

This paper discusses the use of a salvage spiral urethral sling in a very difficult to treat patient population, that is, females who have failed multiple vaginal operations for urinary incontinence. The authors provide an excellent technical analysis and state that when using this technique they are able to salvage approximately three out of four. Of interest is that they describe the use of both autologous fascia as well as synthetic graft. Operative tactics are described in the event of a bladder injury at the time of dissection (laterally placed spiral sling); this is very valuable in view of the potential for injury during the periurethral dissection in this patient population with a history of multiple surgeries. In addition, the authors discuss the use of this operation as opposed to the use of artificial urinary sphincter. Given the success rate of this operation mirrors that reported for artificial urinary sphincter in female patients, it has a potential to achieve a great deal of popularity in this very difficult to treat population (1).

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### Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder

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*J Urol.* 2010; 183: 234-40

**Purpose:** The Overactive Bladder Innovative Therapy Trial during phase 1 was a randomized trial demonstrating comparable effectiveness of percutaneous tibial nerve stimulation and extended-release tolterodine during 12 weeks of therapy for frequency, nocturia, urgency, voided volume and urge incontinence episodes. In this second phase of the Overactive Bladder Innovative Therapy Trial we assessed the sustained therapeutic efficacy of percutaneous tibial nerve stimulation in subjects with overactive bladder during 1 year.

**Materials and Methods:** After 12 weeks subjects randomized to weekly percutaneous tibial nerve stimulation with Urgent((R)) PC were offered an additional 9 months of treatment with assessments at 6 and 12 months from baseline. Outcome measures included voiding diary data, overactive bladder questionnaires, global response assessments and safety assessments.

Results: A total of 33 percutaneous tibial nerve stimulation responders continued therapy with 32 and 25 subjects completing 6 and 12 months of therapy, respectively. Subjects received a mean of 12.1 treatments during an average of 263 days, with a mean of 21 days (median 17) between treatments. Subject global response assessments showed sustained improvement from 12 weeks at 6 and 12 months, with 94% and 96% of responders, respectively. At 12 months mean improvements from baseline included a frequency of 2.8 voids daily ( $p < 0.001$ ), urge incontinence of 1.6 episodes daily ( $p < 0.001$ ), nocturia with 0.8 voids ( $p < 0.05$ ) and a voided volume of 39 cc ( $p < 0.05$ ). Overactive bladder questionnaire symptom severity was significantly improved from 12 weeks to 12 months ( $p < 0.01$ ) as well as from 6 to 12 months ( $p < 0.01$ ). No serious adverse events occurred.

Conclusions: Statistically significant overactive bladder symptom improvement achieved with 12 weekly percutaneous tibial nerve stimulation treatments demonstrates excellent durability through 12 months. The durability of response demonstrates the effectiveness of percutaneous tibial nerve stimulation as a viable, long-term therapy for overactive bladder.

### Editorial Comment

In this study, the authors reviewed the response of patients to percutaneous tibial nerve stimulation (TTNS) over a one year time period. Of the 44 subjects enrolled in the trial, 35 responded to the therapy and of those 35 patients, 33 chose to continue on with the treatment. As noted by the authors, this trial identified that the symptom improvements obtained after the initial 12 treatments were able to be continued with routine ongoing therapy. The authors identified that a longitudinal 30 minutes session every 3 weeks would help keep the symptomatic response durable.

This is an important paper to review especially in view of the increasing popularity of this technology for the treatment of the overactive bladder. Its efficacy, when used with patients who are refractory to medication, raises the consideration for use as a first line therapy. The fact that after the initial 12 weeks sessions, a treatment every three weeks sustains the symptoms makes it an attractive alternative to daily anti-cholinergic therapy. The economic comparisons of the two long term results will be very interesting. Also exciting is the potential use for patients in the institutional setting in which the side effects of anti-cholinergics such as cognitive disorder, xerostomia, and constipation could be avoided by an every 3 week bedside treatment.

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## PEDIATRIC UROLOGY

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### **A multicenter, randomized, controlled trial of transureteral and shock wave lithotripsy -- which is the best minimally invasive modality to treat distal ureteral calculi in children?**

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J Urol. 2010; 184: 1106-9

**Purpose:** Since there is insufficient evidence to determine the best treatment modality in children with distal ureteral calculi, we designed a multicenter, randomized, controlled trial to evaluate the efficacy and complications of transureteral and shock wave lithotripsy in these patients.

**Materials and Methods:** A total of 100 children with distal ureteral calculi were included in the study. Of the patients 50 were randomized consecutively to undergo shock wave lithotripsy using a Compact Delta II lithotripter (Dornier MedTech, Kennesaw, Georgia), and 50 were randomized to undergo transureteral lithotripsy with holmium laser and pneumatic lithotripter between February 2007 and October 2009. Stone-free, complication and efficiency quotient rates were assessed in each group.

**Results:** Mean +/- SD patient age was 6.5 +/- 3.7 years (range 1 to 13). Mean stone surface was 35 mm(2) in the transureteral group and 37 mm(2) in the shock wave lithotripsy group. Stone-free rates at 2 weeks after transureteral lithotripsy and single session shock wave lithotripsy differed significantly, at 78% and 56%, respectively ( $p = 0.004$ ). With 2 sessions of shock wave lithotripsy the stone-free rate increased to 72%. Efficiency quotient was significantly higher for transureteral vs shock wave lithotripsy (81% vs. 62%,  $p = 0.001$ ). Minor complications were comparable and negligible between the groups. Two patients (4%) who underwent transureteral lithotripsy sustained a ureteral perforation.

**Conclusions:** In the short term it seems that transureteral and shock wave lithotripsy are acceptable modalities for the treatment of distal ureteral calculi in children. However, transureteral lithotripsy has a higher efficacy rate when performed meticulously by experienced hands using appropriate instruments.

### Editorial Comment

Citing a lack of well-designed randomized controlled trials for the treatment of distal ureteral stones, the authors of this study created a multicenter, randomized, controlled trial, which compared ureteroscopy with extracorporeal shock wave lithotripsy. They enrolled 100 children and randomized 50 of them to ureteroscopy with lithotripsy using primarily a pneumatic lithotripter. The other 50 children underwent shock wave lithotripsy. Success rates were significantly better for the patients who underwent ureteroscopy both at two weeks and at three months. The authors did have two cases of ureteral perforation in the ureteroscopy group, one of which required open surgery to correct. They cited some equipment problems as contributing to these two major complications and one also has to wonder if using a pneumatic lithotripter as opposed to Holmium laser in these patients may have also been a contributing factor. In terms of differences in minor complications, 30 of the patients in the lithotripsy group had some skin bruising and three patients developed "steinstrasse". There was some mucosal tearing noted in two patients in the ureteroscopy group, which required temporary stent placement.

Although surgical experience is not accounted for in this study, certainly this is a factor that will have an impact on success rates and complications for these modalities. The results of this randomized controlled trial favor a ureteroscopic approach to distal stones despite the fact that it is a more invasive procedure by nature. Improved instrumentation for pediatric patients as well as routine use of Holmium laser lithotripsy over a pneumatic lithotripter will likely continue to make this modality a safe and more effective option for distal ureteral stone management in the pediatric population.

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**Impact of epispadias repair on bladder growth in boys with classic bladder exstrophy**

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J Pediatr Urol. 2010; 6: 578-81

**Objective:** Growth of the bladder in children with bladder exstrophy is primarily responsible for later ability to void continently. Improvement in bladder capacity has been noted in some boys following epispadias repair. Does the timing of epispadias repair influence the ability of the bladder to grow?

**Methods:** Data were collected regarding bladder volume measurements, obtained under anesthesia using a standard technique, during yearly follow-up of boys with classic bladder exstrophy. Volume prior to epispadias repair was compared to the next volume measure following repair. Timing of epispadias repair was compared to changes in bladder capacity in 30 boys. Monthly increases in bladder capacity were calculated in boys repaired at < 12 (4), 13-24 (12) and 25-48 (14) months.

**Results:** Patients who had surgery prior to 12 months of age had the highest rate of monthly increase in bladder capacity (2.40 cc/month). Monthly growth rates were 1.91 cc/month for patients repaired at 13-24 months and 1.18 cc/month for those repaired at 25-48 months.

**Conclusions:** Epispadias repair does lead to early increase in bladder capacity in boys with classic bladder exstrophy. The monthly increases in bladder capacity are greater in boys < 12 months. Improvement in bladder volume is less likely when epispadias is repaired after age 29 months.

**Editorial Comment**

This study evaluated the timing of epispadias repair in exstrophy patients with its impact on bladder capacity. The authors retrospectively reviewed all boys undergoing reconstruction, where adequate data were available. The infants underwent routine cystographic evaluation to measure changes in bladder capacity following the initial closure and again 8-16 months following epispadias repair. The authors divided their cohort into three groups: those who underwent epispadias repair prior to 12 months of age; those who were repaired between 13-24 months; and those having reconstruction at 25-48 months of age. They found the greatest increase in capacity over time in those who underwent epispadias repair prior to 12 months of age. Unfortunately, there were only four patients in this cohort. They had larger numbers in the other two groups and both of these showed a trend towards improved bladder capacity with epispadias repair at a younger age.

Although the small number of patients in this study does not lend itself to achieving statistical significance, the data would certainly argue in favor of performing epispadias repair at a younger age. Increasing bladder outlet resistance should improve bladder cycling and allow for improved capacity as the child gets older which will in turn give them the best chance for continence following bladder neck reconstruction. This is the same line of reasoning given by those who favor a complete primary repair at the time of bladder closure.

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## Robotic Assisted Laparoscopic Treatment of Gonadal Vein Syndrome in a Boy

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### ABSTRACT

*Purpose:* Gonadal vein syndrome, with ureteral obstruction and compression by an overlying testicular vein is a controversial and rare diagnosis. Open, laparoscopic, and robot-assisted laparoscopic repairs have been described. We report the first case of robot-assisted gonadal vein ligation for treatment of gonadal vein syndrome in a nine year-old boy.

*Materials and Methods:* A 9 years-old boy presented with a four to six month history of worsening intermittent flank pain, nausea and vomiting. Ultrasound revealed moderate hydronephrosis. Diuretic renography and intravenous pyelography reproduced his pain and demonstrated left-sided hydronephrosis and obstruction. The patient underwent left robot-assisted surgery via a four port approach. The colon was reflected medially. The gonadal vein was dissected off the underlying ureter and ligated using laparoscopic clips. Segmental vein excision and ureterolysis was performed. Inspection of the renal hilum did not reveal any other crossing vessels.

*Results:* Operative time was 94 minutes. The patient was discharged 36 hours after surgery. His hydronephrosis has resolved completely. He remains pain-free nine months after surgery.

*Conclusion:* Robot-assisted laparoscopic vein excision and ureterolysis is a safe option for the management of ureteral obstruction caused by the gonadal vein.

***Int Braz J Urol. 2011; 37 (Video #1): 134\_5***

*Available at: [www.brazjurol.com.br/videos/january\\_february\\_2011/Swana\\_134\\_135video.htm](http://www.brazjurol.com.br/videos/january_february_2011/Swana_134_135video.htm)*

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## EDITORIAL COMMENT

In this video by Swana et al., a novel application of robotic assisted laparoscopic surgery to pediatric urology is very well depicted. This case of gonadal vein syndrome in a symptomatic 9 year old boy highlights that the superior three-dimensional vision and surgical dexterity/range of motion attributable to current robotic surgical technology is in some

ways ideally suited to the surgical management of pediatric urological conditions. As with all evolving surgical technologies, patient / case selection remains the one pivotal criterion best predicting treatment related outcome. I once again applaud these authors on a very illustrative and innovative surgical approach to a case of gonadal vein syndrome.

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## Laparo-Endoscopic Single Site Retroperitoneal Partial Nephrectomy: A Novel Concept

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### ABSTRACT

*Purpose:* Various treatment options are available for small incidentally detected kidney masses, including surveillance, partial nephrectomy and probe ablative therapies. When partial nephrectomy is considered, the procedure can be safely approached laparoscopically, either pure or robot assisted, in experienced hands. Laparo-endoscopic single site (LESS) surgery is a novel approach for partial nephrectomies in well selected cases. In this video, we present our experience with the LESS retroperitoneal partial nephrectomy using the Gelpoint device.

*Material and Methods:* A 63 year old male patient with a BMI of 31, and a history of a T1c prostate cancer, had a 1.5 cm right posterior lower pole renal enhancing mass discovered incidentally on a three phase CT scan. With the patient under general anesthesia, and in a full flank position, a LESS retroperitoneal partial nephrectomy was performed using a 3 cm transverse incision below the tip of the 12th rib. The following instruments and devices were used: A gelpoint device for single incision port of entry, one 10 mm and two 5 mm trocars used through the gelpoint, one 5 mm Olympus HD endoeye flexible tip camera, one roticulator scissors, and one articulating graspers.

*Results:* Operative time, EBL, and hospital stay were 1 hour, 5 ml, and 23 hours, respectively. The pathology result confirmed a benign hemorrhagic cystic mass. The visual analog scale (0-10) for pain at recovery, 6 hours post op, and 23 hours post op was 5, 3, and 1 point, respectively. The patient tolerated clear liquids and regular diet at 6 and 16 hours, after the procedure. At one month of follow-up, the patient is asymptomatic and practically scarless.

*Conclusions:* LESS retroperitoneal partial nephrectomy is safe and feasible in selected cases such as small exophytic posterior renal masses. The retroperitoneal approach avoids mobilization of the colon and kidney to access the posterior surface. Instrument clashing, limited range of motion, and CO2 leakage, can be some difficulties encountered during single port retroperitoneal surgery. However, the Gelpoint device gives a great seal in the flank position and allows the relocation of trocars, without loss of CO2 pressure, to prevent instrument clashing during different parts of the procedure.

***Int Braz J Urol. 2011; 37 (Video #2): 136\_7***

*Available at: [www.brazjurol.com.br/videos/january\\_february\\_2011/Rodriguez\\_136\\_137video.htm](http://www.brazjurol.com.br/videos/january_february_2011/Rodriguez_136_137video.htm)*

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## EDITORIAL COMMENT

In this novel video by Rodriguez and colleagues, a novel approach for a small exophytic renal lesion is presented. Since the first laparoscopic single site surgery (LESS) report in the urological literature by Rane in 2007, different urological procedures including pyeloplasty, renal cryotherapy, adrenalectomy, varicocelectomy, ureterolithotomy have been described (1). This approach uses a single surgical access following the same general principles of pure laparoscopic surgery, with its inherent benefit of minimal surgical trauma. Previously, White et al. described eight LESS retroperitoneal procedures including one partial nephrectomy (2). Aaron et al. reported 5 partial nephrectomy using a transperitoneal (trans-umbilical) LESS approach using a 2 mm port in the axillary line (hybrid technique) (3). Recently, Cindolo et al. reported six LESS cases using a transperitoneal approach, all performed without hilar clamping, one of which required conversion to a standard laparoscopic approach to control bleeding and two necessitating an extra port for renal parenchyma suturing and liver retraction (4).

Single port surgery is considered minimally invasive laparoscopy, and is an alternative to standard laparoscopy in appropriately selected cases. It however remains a technically challenging procedure even for experienced laparoscopists. Instruments for LESS are rapidly evolving in order to avoid clashing and compensate for their limited range of motion. In this regard, robotic technology is trying to eliminate these current limitations.

It remains that partial nephrectomy is a very challenging procedure when a minimally invasive approach is chosen. In this regard, it is imperative to have careful patient selection when a new technique such as this is employed. Carefully chosen cases such as the one shown in the present video by Rodriguez et al. can translate into excellent peri- and postoperative outcomes. Future randomized trials comparing pure laparoscopic and LESS surgery will help delineate the role and merit of this technique. At the present time, careful patient selection remains the key factor predicting a favorable outcome with these novel new surgical techniques to the small enhancing renal mass.

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- Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. *Int Braz J Urol.* 2002; 28:291-301.
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**Conclusions** must be strictly based on the study findings.

**References** should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

**The Abstract** must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

### **NOTE:**

Recent issues of the *International Braz J Urol* must be observed concerning the presentation form of the manuscript.

# International Braz J Urol

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## MANUSCRIPT CHECKLIST

The authors should observe the following checklist before submitting a manuscript to the **International Braz J Urol**

- The sequence of manuscript arrangement is according to the Information for Authors.
- The Article is restricted to about 2,500 words and 6 authors.
- Abbreviations were avoided and are defined when first used and are consistent throughout the text.
- Generic names are used for all drugs. Trade names are avoided.
- Normal laboratory values are provided in parenthesis when first used.
- The references were presented according to the examples provided in the Information for Authors. The references were numbered consecutively, following the sequence that they are mentioned in the text. They were identified in the text using Arabic numeral in parenthesis. The names of all authors were provided. When exist more than six authors, list the first six authors followed by et al. The initial and the final pages of the reference should be provided. The number of references must be accordingly to the informed in the Instructions for Authors, depending on the type of manuscript.
- The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.
- Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.
- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
- A corresponding author with complete address, telephone, Fax, and E-mail are provided.
- A submission letter and a disclosure form, signed by all authors, are included.
- The authors should included written permission from publishers to reproduce or adapt a previously published illustrations or tables.
- Conflict of Interest** – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, is clearly disclosed in the manuscript.
- Check that each figure is cited in the text. The illustrations are not merged in the text.**
- The photographs are supplied as TIFF or JPG files and saved at a resolution of 300 dpi (dots per inch) at final size.
- The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, **not embed in Word or PowerPoint.**
- A list of abbreviations is provided.

## UROLOGICAL CALENDAR

### **26th Annual EAU Congress**

Vienna, Austria

**March 18 – 22, 2011**

E-mail: [info@eauvienna2011.org](mailto:info@eauvienna2011.org)

Website: [www.eauvienna2011.org](http://www.eauvienna2011.org)

### **ESU organised courses, HOT, Education and Innovation at the time of the 26th EAU Annual Meeting**

Vienna, Austria

**March 18 – 22, 2011**

E-mail: [esu@uroweb.org](mailto:esu@uroweb.org)

Website: [www.uroweb.org](http://www.uroweb.org)

### **12th International EAUN Meeting**

Vienna, Austria

**March 19 – 21, 2011**

E-mail: [info@congressconsultants.com](mailto:info@congressconsultants.com)

Website: [www.eauvienna2011.org/12th-eaun-meeting](http://www.eauvienna2011.org/12th-eaun-meeting)

### **2nd International Congress of the Society of Cross- Border Reproductive Care**

Florence, Italy

**March 24 – 27, 2011**

E-mail: [mfridenzon@paragon-conventions.com](mailto:mfridenzon@paragon-conventions.com)

Website: [www.icgrt.com/](http://www.icgrt.com/)

### **International Course on Pain Medicine (ICPM 2011)**

Porto, Portugal

**March 31 – April 3, 2011**

E-mail: [icpm@icpm.net](mailto:icpm@icpm.net)

Website: [www.icpm.net](http://www.icpm.net)

### **36th Annual Meeting American Society of Andrology**

Montreal, Canada

**April 2 – 5, 2011**

E-mail: [info@andrologysociety.org](mailto:info@andrologysociety.org)

Website: [www.andrologysociety.org/meetings/](http://www.andrologysociety.org/meetings/)

### **Annual Meeting of the Mexican Society of Urology**

Puerto Vallarta, México

**April 5 – 10, 2011**

E-mail: [smu@wtcmexico.com.mx](mailto:smu@wtcmexico.com.mx)

Website: [www.cmu.org.mx/beta](http://www.cmu.org.mx/beta)

### **18th Annual Scientific Meeting United Kingdom Continence Society**

Bristol, United Kingdom

**April 6 – 8, 2011**

E-mail: [ukcs@indexcommunications.com](mailto:ukcs@indexcommunications.com)

Website: [www.ukcs.uk.net](http://www.ukcs.uk.net)

### **Leading Lights in Urology Meeting**

Lago Maggiore, Italy

**April 7 – 9, 2011**

E-mail: [m.koops@uroweb.org](mailto:m.koops@uroweb.org)

Website: [www.uroweb.org](http://www.uroweb.org)

### **World Congress of Nephrology 2011**

Vancouver, Canada

**April 8 – 12, 2011**

E-mail: [info@wcn2011.org](mailto:info@wcn2011.org)

Website: [www.wcn2011.org/](http://www.wcn2011.org/)

### **Ghent Live Surgery Days**

Ghent, Belgium

**April 10 – 12, 2011**

E-mail: [poli.urologie@uzgent.be](mailto:poli.urologie@uzgent.be)

Website: [www.ghentlivesurgery.com](http://www.ghentlivesurgery.com)

### **2nd Minimally Invasive Urological Surgical Week**

Braga, Portugal

**April 11 – 14, 2011**

E-mail: [sec-pg@ecsaude.uminho.pt](mailto:sec-pg@ecsaude.uminho.pt)

Website: [www.ecsaude.uminho.pt/pg/urology](http://www.ecsaude.uminho.pt/pg/urology)

## **UROLOGICAL CALENDAR** - *continued*

### **Innovating for Continence: The Engineering Challenge - Preconference Workshops**

Chicago, IL, USA

**April 11, 2011**

E-mail: [info@simonfoundation.org](mailto:info@simonfoundation.org)

Website: [www.simonfoundation.org/Meetings\\_](http://www.simonfoundation.org/Meetings_Innovating_April_2011.html)

[Innovating\\_April\\_2011.html](http://www.simonfoundation.org/Meetings_Innovating_April_2011.html)

### **Innovating for Continence: The Engineering Challenge Conference**

Chicago, IL, USA

**April 12 – 13, 2011**

E-mail: [info@simonfoundation.org](mailto:info@simonfoundation.org)

Website: [www.simonfoundation.org/Meetings\\_](http://www.simonfoundation.org/Meetings_Innovating_2011.html)

[Innovating\\_2011.html](http://www.simonfoundation.org/Meetings_Innovating_2011.html)

### **American Association of Genitourinary Surgeons Annual Meeting**

Charleston, South Carolina, USA

**April 13 – 16, 2011**

E-mail: [sheskett@umich.edu](mailto:sheskett@umich.edu)

Website: [www.aagus.org/index.htm](http://www.aagus.org/index.htm)

### **4th Annual European Perspectives in Genitourinary Oncology**

Berlin, Germany

**April 15 – 16, 2011**

E-mail: [meetings@imedex.com](mailto:meetings@imedex.com)

Website: [imedex.com/AppWeb/announcements/A156-01.asp](http://imedex.com/AppWeb/announcements/A156-01.asp)

### **99th Japanese Urological Association Annual Meeting**

Nagoya, Japan

**April 20 – 24, 2011**

E-mail: [jpurol@mb.infoweb.ne.jp](mailto:jpurol@mb.infoweb.ne.jp)

Website: [www.urol.or.jp/en/index.html](http://www.urol.or.jp/en/index.html)

### **National Congress of the Serbian Association of Urology**

Belgrade, Serbia

**April 21 – 23, 2011**

E-mail: [urologcl@eunet.rs](mailto:urologcl@eunet.rs)

Website: [www.uas.org.rs](http://www.uas.org.rs)

### **ESU organised course at the time of the national congress of the Serbian Association of Urology**

Belgrade, Serbia

**April 22, 2011**

E-mail: [esu@uroweb.org](mailto:esu@uroweb.org)

Website: [www.uroweb.org](http://www.uroweb.org)

### **22nd Annual Congress of the European Society for Paediatric Urology (ESPU)**

Copenhagen, Denmark

**April 27 – 30, 2011**

E-mail: [secretary@espu.org](mailto:secretary@espu.org)

Website: [www.espu2011.org/](http://www.espu2011.org/)

### **14th Iranian Urological Association Congress (IUA)**

Tehran, Iran

**April 28 – May 1, 2011**

E-mail: [info@iuanet.org](mailto:info@iuanet.org)

Website: [www.iuanet.org/Edefault.aspx](http://www.iuanet.org/Edefault.aspx)

### **Annual Meeting American Society of Paediatric Nephrology**

Denver, USA

**April 30 – May 3, 2011**

E-mail: [info@aspneph.com](mailto:info@aspneph.com)

Website: [www.pas-meeting.org/2011Denver/default.asp](http://www.pas-meeting.org/2011Denver/default.asp)

## **XXXIII BRAZILIAN CONGRESS OF UROLOGY**

November 22 - 26, 2011 - Florianópolis, SC, Brazil