

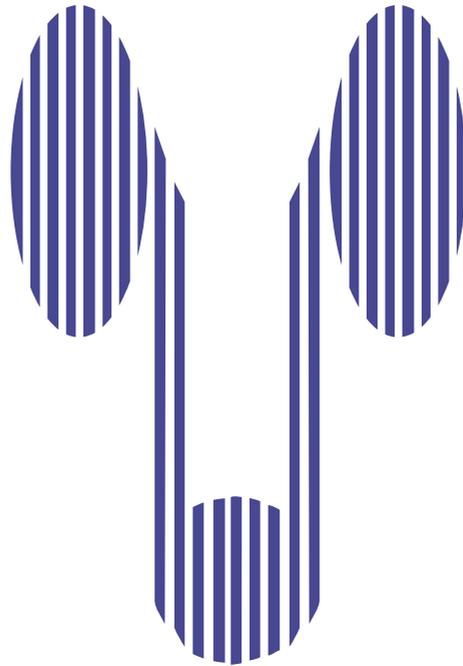
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EDITOR'S COMMENT

The November - December 2006 issue of the International Braz J Urol presents interesting contributions from different countries, and as usual, the Editor's Comment highlights some papers.

Doctor Romero and co-workers, from The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, presented on page 631 their experience with laparoscopic-assisted nephroureterectomy for upper tract transitional cell carcinomas after radical cystectomy and urinary diversion. After studying seven patients the authors found that the mean operative time was 305 minutes with significant difficulty for excision of the ureter from the urinary diversion. The procedure can be performed safely in properly selected cases but does not yield the usual benefits seen with other laparoscopic renal procedures. Doctors Colombo and Gill, from Cleveland Clinic, Ohio, USA, provided editorial comment on this paper.

Doctors Pertia and Managadze from the National Center of Urology, Tbilisi, Georgia, analyzed on page 640 the institutional experience with simple enucleation for the treatment of small renal tumors for elective indications. They studied 30 patients with a median follow-up of 71 months. The pathological analysis showed that 70% (21 of 30) of tumors were pT1a, 26.7% (8 of 30) pT1b and 3.3 % (1 of 30) pT3a. The median tumor size was 3.7 cm (3.0 - 5.5 cm). The authors concluded that simple tumor enucleation is a safe and acceptable approach. It provides excellent long-term progression-free and cancer specific survival rates, and is not associated with an increased risk of local recurrence compared to partial nephrectomy. Doctor Soloway, from the University of Miami, Florida, USA and Doctors Joniau and Van Poppel, from University Hospital Leuven, Belgium, provided interesting editorial comments on this paper.

Doctor Ghalayini and colleagues, from Jordan University of Science & Technology, Irbid, Jordan, compared on page 656 the efficacy of extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) for the treatment of distal ureteral calculi with respect to patient satisfaction. In a prospective study they analyzed 212 patients with solitary, radiopaque distal ureteral calculi treated with ESWL (n = 92) or URS (n = 120). Patient and stone characteristics, treatment parameters, clinical outcomes, and patient satisfaction were assessed for each group. It was found that URS is more effective than ESWL for the treatment of distal ureteral calculi. ESWL was more often performed on an outpatient basis, and showed a trend towards less flank pain and dysuria, fewer complications and quicker convalescence. Patient satisfaction was significantly higher for URS according to the questionnaire used in this study. Doctor Ather, from Aga Khan University, Karachi, Pakistan, Doctor Ceylan, from Yuzuncu Yil University, Van, Turkey and Doctor Anderson, from University of Minnesota, Edina, Minnesota, USA, provided excellent editorial comments on this paper.

Doctors Lazzeri & Spinelli, from Casa di Cura Santa Chiara Firenze, Italy, reviewed on page 620 the alternative to antimuscarinic agents for the management of overactive bladder (OAB). They reviewed the pathophysiology of micturition reflex, the current therapies for OAB and the rationale for alternative treatments. They also critically address the potential use of medications targeting the central nervous system and the primary sensory nerves of the bladder wall, the use of agonists of nociceptin/orphanin protein receptor and reported the results obtained by intradetrusor injection of botulinum toxin.

EDITOR'S COMMENT - *continued*

Doctor Ligure and colleagues, from Federal University of Sao Paulo, Brazil, evaluated on page 689 the role of elective appendicovesicostomy in association with Monfort abdominoplasty to avoid urinary tract infection (UTI) and renal damage in the postoperative follow-up of patients with prune belly syndrome. They followed 4 patients operated in one institution (Monfort, orchidopexy and Mitrofanoff) and compared them to 2 patients treated similarly, but without an appendicovesicostomy, in a second institution. The data suggest that no morbidity was added by the appendicovesicostomy to immediate postoperative surgical recovery and that this procedure may have a beneficial effect in reducing postoperative UTI events and their consequences by reducing the postvoid residuals in the early abdominoplasty follow-up. Doctor Denes, from University of Sao Paulo, Brazil and Doctor Monti, from Triangulo Mineiro Federal University, Minas Gerais, Brazil, provided editorial comments.

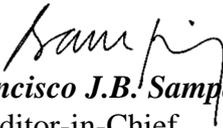
Doctor Martins from Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, presented and illustrated by the first time on page 713 an interesting surgical technique of mouse kidney transplantation using an anti-reflux system (modified extravesical ureteroneocystostomy). The author demonstrated that although technically demanding, this procedure is feasible and may reduce the incidence of urine leakage. Doctor Flechner, from Cleveland Clinic Foundation, Ohio, USA and Doctor Schumacher from Karolinska University Hospital, Stockholm, Sweden, provided editorial comments on this article.

As everybody noted, during 2006 the International Braz J Urol continued to grow in circulation, acceptance and adherence to scientific standards.

This growth is thanks to our Board of Consulting Editors, which is composed by prominent individuals in their areas, including urologists and scientists from more than 25 countries, all of them with significant scientific production and compromised with our Journal. During 2006, we received articles from 23 different countries for evaluation, which confirms the already known international characteristic of our Journal. Also, during the year of 2006 we have the contribution of 374 ad-hoc reviewers, from 43 countries, reviewing articles and making editorial comments. Many of these reviewers evaluated two or more articles during this year, and we deeply acknowledge these overcommitted colleagues for accepting to collaborate and participate in that venture.

Since January 2006, the International Braz J Urol, in addition to be the official Journal of the Brazilian Society of Urology – SBU, is the official Journal of the Confederación Americana de Urologia - CAU, a society which represents a total of 21 Latin American and Iberian countries through their official societies. The Journal is mailed regularly to all urologists from Brazil and to urologists that are members of the official Urological societies from all countries of South and Central America. Also, urologists from Portugal, Spain, other European Countries, and USA receive the International Braz J Urol.

In addition to the printed version, which has a circulation of 6,000 copies per issue and reaches more than 60 countries, the electronic version of our Journal has been receiving around 30,000 visits on-line every month, from more than 110 different countries, and these figures make the International Braz J Urol one of the most read urological journals. As everybody knows, in addition to a high-qualified Editorial Board, the success of a scientific Journal is measured by the number of readers, papers submitted and citations. I do hope that all of you will continue to collaborate with our Journal to expand its importance and position in the urologic literature.


Dr. Francisco J.B. Sampaio
Editor-in-Chief

The Challenge of Overactive Bladder Therapy: Alternative to Antimuscarinic Agents

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ABSTRACT

Contemporary, the management of overactive bladder (OAB), a medical condition characterized by urgency, with or without urge urinary incontinence, frequency and nocturia, in absence of genitourinary pathologies or metabolic factors that could explain these symptoms, is complex, and a wide range of conservative treatments has been offered, including bladder training, biofeedback, behavioral changes, oral or intravesical anticholinergic agents, S3 sacral neuromodulation and peripheral electrical stimulation. Clinical efficacy of these treatments remains an open issue and several experimental and clinical studies were carried out in the last years improving the results of medical treatment.

Here we review the pathophysiology of micturition reflex, the current therapies for OAB and the rationale for alternative treatments. Furthermore we critically address the potential use of medications targeting the central nervous system (CNS) and the primary sensory nerves of the bladder wall, we review the use of agonists of nociceptin/orphanin protein (NOP) receptor and finally we report the results obtained by intradetrusor injection of botulinum toxin.

Key words: *overactive bladder; voiding dysfunction; pharmacotherapy; receptor; orphanin fq; botulinum toxins*
Int Braz J Urol. 2006; 32: 620-30

INTRODUCTION

Overactive bladder (OAB) is a medical condition characterized by urgency, with or without urge urinary incontinence, frequency and nocturia, in absence of genitourinary pathologies or metabolic factors that could explain these symptoms (1). This definition represents an important clinical message because in the era of High-Tech medicine, people look for medical help in the same way as in the past as a result of symptoms. The key symptom, which characterizes OAB, is "urgency": the sudden and compelling desire to pass urine, which is difficult to defer.

OAB affects one sixth of European population aged 40 years or over (2) and similar data have

been reported also for United State of America where around one sixth of adults aged 18 years and over have symptoms of OAB; the estimated prevalence is 33 million US residents aged over 18 years (3). Recently Erwin reported a cross-sectional population-based survey of people > 18 years showing that the total prevalence in 4 European countries is 12.2% and confirmed that OAB is a common condition in men and women across all adult age group (4). One third of people with overactive bladder have urge urinary incontinence and large population studies have reported that the prevalence of symptoms of OAB increases with age (5).

The aim of this paper is to address critically the therapy of OAB providing an up-to-dated insight on alternative strategies to antimuscarinics.

PATHOPHYSIOLOGY OF MICTURITION REFLEX

The lower urinary tract serves two main functions: the storage of urine without leakage (storage phase) and the periodic release of urine (voiding phase). During the storage phase the detrusor muscle is relaxed and the outlet region is contracted to maintain continence. During the voiding phase the detrusor muscle contracts and the outlet region relaxes facilitating bladder emptying. These two functions are dependent on central, peripheral autonomic and somatic neuronal pathways and local peripheral factors. During the storage phase the afferent impulses reach the central nervous system (CNS) from the lower urinary tract and afferent activity sends information to the periaqueductal grey of pons. In the pontine tegmentum there are two regions: a medially located one (M-region), which corresponds to Barrington's nucleus or pontine micturition center which is responsible of coordination of micturition reflex (6), and a laterally located one (L-region), which is involved in the storage phase suppressing the bladder contraction and improving external sphincter muscle activity during this phase (7). The emerging development of functional imaging such as single photon emission tomography (SPET), positron emission tomography (PET) and functional MRI showed several sovraspinal-sovrpontine (cortical) areas involved in the micturition reflex, but so far their specific role remains obscure (8-10).

Three different sets of peripheral neuronal systems are involved in the micturition reflex: the parasympathetic system the sympathetic system and the somatic system. The parasympathetic system originates in the sacral level of the spinal cord (S_2 - S_4) and provides an excitatory input to the bladder by the postganglionic nerve terminal release of Acetylcholine (Ach), which excites muscarinic receptors (M_2 , M_3) in the detrusor smooth muscle leading to the bladder contraction. The sympathetic system originates in the thoracolumbar cord (Th_{11} - L_2) and provides an inhibitory input to the bladder by the postganglionic nerve terminal release of norepinephrine (NA) which excites β_3 receptors in the body of the detrusor leading to the bladder relaxation. The

sympathetic system also provides an excitatory input to the urethra smooth muscle by the postganglionic nerve terminal release of norepinephrine (NA) which excites α_1 receptors in the urethra leading to the urethral closure. The somatic system provides an excitatory input to the striated urethral muscle; in this case the motoneurons are located along the lateral border of the ventral horn of the sacral spinal cord, which is known as the Onuf's nucleus. They release Ach, which acts on nicotinic receptors to induce muscle contraction.

Immunohistochemical and morphological studies, which have been conducted on the bladder wall, showed that there are a lot of neuronal terminal endings that do not correspond to cholinergic and adrenergic innervations (11). These nerves, which are non adrenergic - non cholinergic (NANC), are peptide containing fibers and they are selectively sensitive to capsaicin, the pungent ingredient of red peppers, heat and H^+ . They are primary afferents and may play an important role in the regulation of lower urinary tract functions (12). These nerves consist of small myelinated $A\delta$ and un-myelinated C fibers, which are, however, "silent" under normal conditions.

Data from several laboratories have recently shown the importance of peripheral local factors in the regulation of micturition reflex. The bladder urothelium can respond to chemical and mechanical stimuli releasing different mediators, which target the receptors of adjacent sensory nerves (13). Birder introduced the concept of "neuron-like properties" of urothelium. Urothelium responds to stretch, during the filling phase of micturition reflex, by increasing the size of apical umbrella cells and by releasing mediators, which activate sensory fibers (14). Finally several investigators suggest a regulatory role for interstitial cells, which are part of a "vesical module" consisting of nerves, smooth muscle cells and interstitial cells. It is thought that this module may receive diverse inputs and may be able to modulate local reflex or activity (15).

OAB may result from increased bladder afferent activity, decreased capacity to handle afferent information or decreased suprapontine inhibition in the CNS, and increased peripheral sensibility to release mediating transmitters. This last situation,

known as “bladder oversensitivity”, could originate from the release of neurotransmitters by urothelium or sensitization of sensory nerves by paracrine pathways. The CNS as well as the periphery may represent the target for a new class of medications against OAB.

CURRENT THERAPIES FOR OVERACTIVE BLADDER

Anticholinergics, which antagonist Ach for the muscarinic receptors, are first line pharmacological treatment for overactive bladder. The indication for the treatment of OAB derives from a high level of evidence (Level-1) and high grade of recommendation (Grade-1) (16). Anticholinergics produce significant symptom improvements in OAB syndromes when they are compared to a placebo and the number of anticholinergic drugs available on the market is increasing. However, the debate about the pathophysiological rationale and the clinical use of antimuscarinic agents remains an unsolved issue.

Herbison reported a systematic review of anticholinergic drug treatment compared to a placebo therapy in the treatment of overactive bladder as a result from randomized controlled trials (17). He found that those patients receiving active treatment were more likely to be subjectively improved and they had about one leakage episode less in 48 hours than those taking placebo. Urodynamic assessment showed larger increase in maximum cystometric capacity in those receiving active treatment and the volume at first contraction increased more in the drug group than in the placebo group. Dry mouth was the most frequently reported side effect. Herbison concluded that although statistically significant, the differences between anticholinergic drugs and placebo were small, apart from the increased rate of dry mouth in patients receiving active treatment. For many of the outcomes studied, the observed difference between anticholinergics and placebo may be of questionable clinical significance.

After the publication of this paper many urologists felt that Herbison had inappropriately written off this class of drugs and that the author had a

preconceived notion about anticholinergics. Chapple et al. carried out a systematic review and a meta-analysis on the effects of antimuscarinic in the OAB therapy (18). His review was planned to assess the safety, tolerability and efficacy of antimuscarinic in the OAB therapy, considering the effects on quality of life (QoL), differences between different antimuscarinics and, finally, addressing criticism of Herbison’s review. Chapple’s review has many differences regarding Herbison’s study. He did a systematic analysis of QoL data, a differentiation between individual antimuscarinics, including active controlled trials and following a “splitting” approach and not a “cumulative” approach. Chapple et al. reported that antimuscarinic formulations, apart from Oxybutynin IR (immediate release) were found well tolerated and no drug was associated with a significant risk of death. Also, in this review dry mouth was the most commonly reported adverse effect, even if other adverse reactions were included (blurred vision, constipation, dyspepsia, nausea, vomiting, urinary retention). Antimuscarinics were able to reduce frequency, urgency episodes by over one episode per day, incontinence by half an episode or more per day and the volume voided per micturition was increased. Finally patients receiving antimuscarinics have greater improvements in QoL than patients on placebo arm. Chapple et al. (18) concluded that there is a quantifiable objective and clinical benefit conferred by antimuscarinics in the therapy of OAB.

However, most of the studies, which were considered in the review, had limitations of evidences such as choice of outcome measure, trial length, restricted population, the high placebo effect and economic issues. For all these reasons, today, many of us are disputing formally and systematically in order to trigger an appropriate response to the question on the rational of use of anticholinergics and for finding alternative therapies.

RATIONALE FOR ALTERNATIVE THERAPIES TO ANTICHOLINERGICS

In the past, many factors discouraged the extensive research on new drugs in the treatment of OAB

or LUTS. The main limitations were due to the complex neuropharmacological arrangement of voiding reflex and sexual function, the simple “easy to accept” idea of antagonistic, parasympathetic cholinergic and sympathetic adrenergic control of the LUT and the complex interrelationship between the voluntary somatic control of visceral reflex and the involuntary components.

In the last 2 decades the neuropharmacology gained advantages from basic science research and the experimental results were translated in the clinical practice. The main advantages were due to the discovery of non-adrenergic - non-cholinergic innervation (NANC) of the LUT (19), the recognition of a multiplicity of neurotransmitters (monoamines, purines, amino acid, peptides and nitric oxide) (11), the concept of co-transmission (nerves release more than one transmitter) and the recognition of the basilar importance of a sub set of sensory nerves which are sensible to capsaicin, the pungent ingredient of red chilli, in the control of micturition reflex (20). Finally, the discovery of a new variety of different receptors, involved in the regulation of sensory nerves' conduction and changes occurring during not only development and ageing but also after trauma or chronic inflammation (neuroplasticity), were basilar for the development of alternative therapies (21-23).

Today CNS, sensory nerves and bladder smooth muscle cells represents the main targets of alternative strategy for OAB.

CENTRAL NERVOUS SYSTEM

Several CNS transmitters/receptors systems, including adrenoceptors, γ -aminobutyric acid (GABA), opioid, serotonin, noradrenaline, dopamine, and glutamatergic receptors are known to be involved in micturition control (24).

Several and different adrenoceptors have been found in the brain and spinal cord. High levels of α_{1A} mRNA have been showed in many hypothalamic nuclei, α_{1A} mRNA and α_{1B} mRNA in amygdala and raphe nuclei and α_{1D} mRNA in the cortex, hippocampus and amygdala. Different studies showed

that i.t. or i.c.v. α_1 antagonists reduced the detrusor overactivity in the spontaneously hypertensive rat, i.t. or i.c.v. tamsulosine inhibits the micturition reflex by the activation of spinal receptors and α_2 agonists produce the activation of micturition reflex by the activation of supraspinal and spinal receptors (25). α_{1A} -, α_{1B} -, and α_{1D} -AR mRNA can be demonstrated in the parasympathetic nucleus in the sacral spinal cord (26) and α_{1d} -AR KO mice vs. wild type controls showed lower voiding frequency, larger bladder capacity and larger voided volumes (27). Naftopidil and tamsulosin both block α -ARs in prostatic smooth muscle, and both agents (especially naftopidil) may also act on the lumbosacral cord (28). It is interesting report that tamsulosin and aftopidil in a 8-week crossover-study on 96 BPH patients decreased the I-PSS for storage symptoms (29). This study suggests that naftopidil is as effective and safe as tamsulosin and both drugs were effective in improving storage and voiding symptoms. However, there was no difference in clinical efficacy or adverse effects between the α_1 AR antagonists with different affinity to α_1 subtypes, α_{1A} and α_{1D} (30).

There has been little interest in developing drugs active on opioid mechanisms for the treatment of bladder disorders, despite the profound inhibitory effects that morphine and analogs have on the micturition reflex. However, tramadol, which is both a μ -receptor agonist and an inhibitor of noradrenaline and serotonin uptake, has been reported to have promising effects on micturition in animal models (31). Tramadol produced the inhibition of detrusor overactivity induced by cerebral infarction in rats and the inhibition of detrusor overactivity induced by apomorphine in rats (32).

Serotonin and its receptors may play an important role in the central regulation of micturition reflex. Exposure to selective serotonin reuptake inhibitors (SSRIs) is associated with an increased risk (15/1000 patients) for developing urinary incontinence especially between the elderly and users of sertraline are at the highest risk (33). Clomipramine treated female rat pups void more frequently than controls, have a lower bladder capacity and show detrusor overactivity. Fluoxetine treatment reverses these effects. Up to date, no convincing documenta-

tion exists whether or not SSRIs are effective in the treatment of OAB, and despite positive acute effects in preclinical models, there are no proof of concept studies showing that subtype selective 5-HT receptor antagonists (5-HT1A, 5-HT7) are effective in the OAB treatment.

In the normal rat, stimulation of GABA receptors, mainly in the central nervous system, inhibits micturition. Antagonism of GABA_B receptors stimulates micturition, suggesting that the receptors are under tonic GABAergic influence. Intrathecally baclofen attenuates oxyhemoglobin induced detrusor overactivity, suggesting that the inhibitory actions of GABA_B receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium (34). Recently experimental studies have demonstrated the inhibitory effect of exogenous gamma-aminobutyric acid (GABA) on micturition. Tigabine inhibits the micturition reflex in rat and its site of action, which may be central (35).

Finally, Kim reported the effects of gabapentin in 14 out of 31 patients with refractory OAB. He found an improvement of clinical parameters with fewer side effects, gabapentin was generally well tolerated, and it can be considered in selected patients an alternative treatment to antimuscarinics.

In conclusion, several promising new principles have been recently investigated, but only few drugs have passed the stage of "proof" of concept.

SENSORY NERVES

Recently, the idea of afferent blockade by targeting afferent nerves that control the micturition reflex has gained the trust of urologists as a potential alternative to current drug therapies. The emerging concept is that it would be more desirable to prevent the micturition reflex that initiates overactive bladder, instead of blocking the contraction of detrusor smooth muscle. The concept of a therapeutic approach through the modulation of the afferent arm of the micturition reflex emerged when investigators studied the effect of capsaicin on sensory nerves. Capsai-

cin targets the transient receptor potential vanilloid-1 (TRPV1), which is expressed on small-to-medium size afferent neurons, which are most of C-type but also in a fraction of A- δ type. The acute exposure to capsaicin depolarizes and excites sensory fibers expressing TRPV1 receptors. This excitation is followed by a refractory period. It means that the repeated, long-term, high dose exposure to capsaicin desensitizes, defunctionalizes and ultimately damages peripheral terminals, which become unresponsive. In other words, the mechanism of action by which capsaicin works is a long lasting reversible suppression of sensory nerve activity and it is dependent on dose, time of exposure and interval between consecutive instillations.

The proof of concept that an inhibitory modulation of urinary bladder afferent nerves could achieve a therapeutic benefit in the treatment of bladder overactivity, was obtained through the intravesical instillation of repeated low concentration doses or single high concentration doses of capsaicin (20). The first experiences were performed in patients with neurogenic detrusor overactivity. De Ridder reported that repeated instillations of intravesical capsaicin was effective in approximately 80% of the patients with bladder overactivity due to spinal cord disease and the beneficial effect lasted 3 to 5 years (36). At the end of the 1990s Lazzeri questioned the efficacy and the safety of capsaicin for the management of detrusor hyperreflexia (37) and Petersen demonstrated, in a placebo controlled crossover study, that intravesical treatment with capsaicin did not show beneficial effects on detrusor hyperreflexia and produced significant reactive changes in the bladder mucosa (38). Lazzeri reported that 12.96% of patients had a significant episode of autonomic dysreflexia during the infusion, 35.18% presented rhythmic detrusor contractions causing the leakage of urine and 96% of the patients with incomplete spinal lesion and bladder sensation reported a warm/burning/painful sensation (39). de Seze, by Bordeaux group, found that the capsaicin side effects were due to alcohol (the vehicle), which were used, sometimes, at the concentration of 30%. When capsaicin was diluted in glucidic acid, intravesical instillation was equally effective with fewer adverse events (40). Owing to the warm/burn-

ing sensation/discomfort that capsaicin produced in subjects with normal sensation and increasing the regulation of non licensed agents, the source of capsaicin mostly having been chemical rather than pharmacological suppliers, was replaced by the pharmaceutically prepared resiniferatoxin (RTX). RTX, obtained from a cactus species of the genus Euphorbia, *Euphorbia resinifera*, is an ultra potent capsaicin analogue to a thousand fold the selective C-fiber neurotoxicity of capsaicin for comparable pungency and with fewer side effects. Against a strong scientific background of its demonstrated mode of action in animal models, the use of this agent therefore held out the promise of an effective “de-afferenting” instillation with little discomfort. However, the reality to date has unfortunately been otherwise. Following early positive reports of its effectiveness in both neurogenic (41,42) and idiopathic detrusor overactivity (43) large scale placebo controlled multicentric clinical trials in Europe and the US were initiated to examine the efficacy of the agent in patients with neurogenic bladder. During the course of these studies it became apparent, to those involved in the trials, that many patients were not responding at all, which led to a review of the study procedures and the recognition of the possible loss of active drug availability due to the adsorptive properties of RTX to plastic. Immunohistochemical evidence showed that responders had a demonstrable reduction of nerve density of suburothelial innervations, with a parallel reduction in the expression of TRPV1 and P2X receptors (44,45) of these nerves.

Other centers continued to examine the efficacy of RTX in detrusor overactivity (46,47) and because of the known effect of RTX on afferent innervations, a study looked at its efficacy in conditions of bladder pain or interstitial cystitis (48). Encouraged by positive findings, a pharmaceutical company recently funded a large scale placebo controlled study using RTX to treat interstitial cystitis. Unfortunately the reported benefits were no greater in the active treatment than the placebo group and it therefore seems unlikely that a pharmaceutical preparation of RTX will continue to be made available unless there is some further development in this field.

Recently experimental and clinical evidence has showed that the inhibitory system nociceptin/orphanin (NO) FQ - nociceptin/orphanin protein (NOP) receptor, may play an important role in the modulation of micturition reflex. Nociceptin inhibits the activity of TRPV1-expressing neurons at the peripheral level by the activation of a specific G-protein coupled receptor named nociceptin orphan peptide (NOP) receptor (49). In a pilot, uncontrolled study, the intravesical infusion of N/OFQ increased the bladder capacity in a selected group of patients suffering from neurogenic detrusor overactivity, but not in normal subjects (50). These findings were replicated in a placebo-controlled randomized study suggesting that NOP receptor agonists modulate the micturition reflex in humans and they could represent a suitable alternative to the treatment of OAB to oral antimuscarinics (51).

BOTULINUM TOXIN

Botulinum toxin (BTX) is a complex protein, produced by the anaerobic bacterium *Clostridium botulinum*. Previously known only as a cause of a serious and often fatal paralysis acquired through ingestion of contaminated food, the neuromuscular blocking effect of the toxin has been thought that might alleviate muscle spasm due to excessive neural activity of central origin. Local injections of BTX have been showed effective in the treatment of strabismus, essential blepharospasm, and hemifacial spasm and further studies indicate that BTX injections also can provide useful symptomatic relief in a variety of other conditions characterized by involuntary spasms of certain muscle groups, notably in focal or segmental dystonia including spasmodic torticollis, oromandibular dystonia (orofacial dyskinesia, Meige syndrome), and spasmodic dysphonia. Recently the unlicensed use of toxin in the treatment of lower urinary tract (LUT) conditions has been described. (52). LUT disorders are characterized by detrusor sphincter dyssynergia (53,54), detrusor overactivity neurogenic detrusor overactivity (NDO) (55) and also idiopathic detrusor overactivity (IDO).

Botulinum toxin is thought to work by cleaving a synaptosome-associated protein, SNAP-25, thereby blocking the presynaptic release of acetylcholine at the neuromuscular junction. This protein is part of SNARE complex, which is vital for vesicular exocytosis and relies on Ach. It is important to remind that, after exposure to botulinum toxin, neuronal death does not occur, but the phenomenon of re-sprouting of axons, leading to new synaptic contacts, also occurs and these presumably account for the return to muscular function, which is observed after a number of months (56). The re-sprouting of axons might also play a role in hyperactivity of muscular function or reduction of compliance in case of the bladder injection repetition.

In the last year several investigators suggested that BTX might affect urothelium/suburothelium sensory innervations. BTX-A has been found to reduce pathologically elevated levels of neurotransmitters including ATP, to decrease the number of suburothelial afferent neurons expressing purinergic receptors and to reduce urgency (57,58). The exact mechanism of action on the afferent pathway remains unknown.

Following the remarkable efficacy seen in studies with NDO, a number of researchers have investigated BTX use in patients suffering from antimuscarinic refractory OAB. Chancellor was the first to investigate the effect of BOT in a group of patients with overactive bladder refractory to other conservative treatments (59). Rapp investigated the effects of injection of botulinum toxin in thirty-five patients (29 women and 6 men) with frequency, urgency, and/or urge incontinence (60). The patients received 300 UI of BTX-A injected transurethrally at 30 sites within the bladder. Overall, 21 (60%) of 35 patients reported slight to complete improvement of voiding symptoms after 3 weeks. Among the initial responders followed up for 6 months an improvement of quality of life was reported in most patients with fewer side effects. Due to the increased understanding of the role of the urothelium in OAB, Kuo assessed sub-urothelial injections of BTX (61). It was found that although this method of administration was more effective than detrusor injections, there was impaired bladder sensation and voiding

efficiency. Voiding difficulty was reported by 75% of patients, and 30% required catheterization. This suggests that blockade of detrusor contractility through sub-urothelial sensory fibers was much more pronounced than at neuromuscular junctions or that only a small amount of diffusion of BTX from the detrusor to the sub-urothelium occurs following detrusor injection. More recently Schulte-Baukloh performed BTX injections in patients with refractory OAB symptoms but with no evidence of DO on prior urodynamics (62). Significant improvements were seen in symptoms scores, bladder diary and urodynamic parameters. In this group of patients no increased PVR or need for CISC was noted even with a dose of 300 UI of BTX. In order to avoid acute urinary retention or PVR, all patients had 50-75 UI of the BTX concurrently injected into the external sphincter without increasing stress incontinence rate.

Several studies supported the BTX as promising therapy in urological disease conditions as previously described, however additional investigations, including controlled clinical trials, are needed. Further studies of the mechanism of action of botulinum toxin and its pharmacotherapeutics are also needed and international standardization of measures of biological activity of botulinum toxin is requested. We strongly suggest that for most of urological indications, botulinum toxin should be used by committed interdisciplinary teams of physicians and related health care professionals with appropriate instrumentation to assess the clinical beneficial as well as objective and sub clinical side effects. The long-term effects of chronic treatment with botulinum toxin remain unknown. Prolonged follow-up is necessary in patients on maintenance therapy and an international independent database should be established.

CONCLUSION

Generally new therapies are supposed to be better than the treatment they replace and not to induce any side effects. Studies of an alternative treatment to antimuscarinics for overactive bladder (OAB)

are more likely to cite preliminary studies reporting positive results than equally valid studies, which use the same compounds, with disappointing results. Most of us, generally, have an unwarranted optimism in the efficacy of new therapies and it might represent, or be called, an optimism bias. This mental position, with regard to a state of research in a specific field i.e. overactive bladder therapy, has several serious implications. One is the creation of potentially unrealistic expectations, for both patients and clinicians, of the likely benefits of new treatments such as botulinum toxin. All of us should make emerge a crucial empirical question: what is the prior probability, on average, of a proposed new treatment for OAB or urge urinary incontinence being superior to antimuscarinic agent treatments? The available data seems to suggest that new treatments (vanilloids, nociceptin/orphanin FQ, botulinum toxin) are equally likely to be inferior to standard treatments as they are to be superior. The issue, which remains unsolved, is the fact that new therapies are generally adopted in patients refractory to anticholinergics and this represents a clear selection bias. Furthermore, clinicians need to be aware that optimism is usually both unwarranted and counterproductive when there is uncertainty about the long-term effects of treatments, and of the resulting need to address this uncertainty in clinical trials. On the contrary, in some circumstances it runs the risk of deterring participation in clinical trials designed to reduce genuine and important uncertainties about the effects of treatments, and of discouraging replication of apparently promising early studies. Until these issues are addressed there must remain doubts about whether clinicians involved in trials, which use new drugs, are genuinely observing the outcome and they maintain the ethical requirement of uncertainty.

CONFLICT OF INTEREST

The authors have no conflict of interest. The authors perspective on this topic is a personal one and of necessarily selective bibliography, and cannot do justice to the vast literature about this field.

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Laparoscopic-Assisted Nephroureterectomy after Radical Cystectomy for Transitional Cell Carcinoma

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ABSTRACT

Objective: To report our experience with laparoscopic-assisted nephroureterectomy for upper tract transitional cell carcinomas after radical cystectomy and urinary diversion.

Materials and Methods: Seven patients (53-72 years-old) underwent laparoscopic-assisted nephroureterectomy 10 to 53 months after radical cystectomy for transitional cell carcinoma at our institution. Surgical technique, operative results, tumor features, and outcomes of all patients were retrospectively reviewed.

Results: Mean operative time was 305 minutes with a significant amount of time spent on the excision of the ureter from the urinary diversion. Estimate blood loss and length of hospital stay averaged 180 mL and 10.8 days, respectively. Intraoperative and postoperative complications occurred in two patients each. There was one conversion to open surgery. Pathology confirmed upper-tract transitional cell carcinoma in all cases. Metastatic disease occurred in two patients after a mean follow-up of 14.6 months.

Conclusions: Nephroureterectomy following cystectomy is a complex procedure due to the altered anatomy and the presence of many adhesions. A laparoscopic-assisted approach can be performed safely in properly selected cases but does not yield the usual benefits seen with other laparoscopic renal procedures.

Key words: carcinoma, transitional cell; cystectomy; laparoscopy; nephrectomy; recurrence; reoperation

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INTRODUCTION

Nephroureterectomy (NU) is the treatment of choice for high grade, invasive, or recurrent transitional cell carcinoma (TCC) of the upper urinary tract (UUT). Since the first laparoscopic NU was performed in 1991, (1) several series have demonstrated the safety and efficacy of the procedure, (2-6) with the benefits of decreased hospitalization, return to activity and pain

requirement. Nephroureterectomy following cystectomy is a very complex procedure due to the need for complete ureterectomy in the presence of many adhesions and an altered anatomy. This requires extensive enterolysis and dissection in a previously operated site to allow for removal of the ureter from the urinary diversion. There is limited data on open removal and no published data on laparoscopic NU for UUT TCC following cystectomy and urinary

diversion. The objective of this study is to report our experience with laparoscopic-assisted NU for UUT TCC after radical cystectomy.

MATERIALS AND METHODS

In 2003 and 2005, seven patients previously treated with radical cystectomy underwent laparoscopic-assisted NU for UUT TCC. Individual characteristics of the patients and the features of the primary bladder tumors are summarized in Tables-1 and 2, respectively. Cystectomy was performed for BCG-refractory carcinoma in situ (CIS) of the urinary bladder in four patients, recurrent superficial high grade TCC in two, and muscle-invasive disease in one.

Evaluation after cystectomy consisted of physical examination, chest X-ray, and urine cytology every 3-4 months in the first and second years, and at 6-month intervals for up to 5 years, followed by yearly exams. The upper tract was surveyed by intravenous urography (IVU), computed tomography (CT), conduitography and retrograde pyelography, and/or conduitoscopy and ureteroscopy every 6-12 months in the first year, and then yearly or when clinically indicated. Patients with a suspected upper tract tumor were biopsied, and in highly suspicious cases in which retrograde ureteroscopy was not possible were evaluated through nephroscopy, and antegrade pyelography and ureteroscopy.

Indications for NU in patients with a normal contralateral kidney included high-grade biopsy-proven TCC recurrences in three patients, and

Table 1 – Epidemiologic and clinical features of the patients.

Patient	Age	Sex	Predisposing Factors	Co-Morbidities	BMI
1	65	Male	Positive for tobacco	Asthma, atherosclerosis, status post-angioplasty	26.0
2	53	Male	Positive for tobacco	None	34.1
3	68	Female	Negative	Asthma, cardiac arrhythmia	26.0
4	71	Male	Positive for tobacco, benzidine, and components of the rubber making industries	Thyroid disease, urolithiasis, cardiac disease, status post-percutaneous nephrolithotomy, coronary artery bypass, cholecystectomy, appendectomy, and herniorrhaphy	25.9
5	72	Male	Positive for tobacco	Thyroid disease, and hypertension	32.4
6	69	Male	Positive for tobacco	Cardiac disease (status-post coronary artery bypass and repair of aortic aneurysm)	27.7
7	54	Female	Positive for tobacco	Thyroid disease, status post-cholecystectomy	30.6

BMI = body mass index.

Table 2 – Characteristics of bladder tumors treated with radical cystectomy.

Pt. N. Sex Age	Previous Intravesical Chemotherapy	Multifocality	Stage	Grade	Plus Ca In Situ	Prostatic Urethra Involvement	Ureteral Status	Margin Status	Urinary Diversion	Time from Initial Diagnosis to Cystectomy (Months)	Time from Cystectomy to UUT TCC (Months)
1 M 65	None	Multifocal	T2 N0	High grade	Yes	No	Ca in situ (left)	Positive (left ureter)	Ileal conduit	2	15
2 M 53	BCG	Multifocal	T1 N0	High grade	Yes	Yes	Ca in situ (bilateral)	Positive (right and left ureters)	Ileal conduit	8	22
3 F 68	BCG, Thiotepa	Multifocal	T1 N0	High grade	Yes	–	Ca in situ (right)	Positive (right ureter)	Ileal conduit	4	10
4 M 71	BCG, Mitomycin	Multifocal	T1 N0	High grade	Yes	Yes	Ca in situ (bilateral)	Negative	Orthotopic neobladder	3	17
5 M 72	BCG	Multifocal	T1 N0	High grade	Yes	Yes	Ca in situ (bilateral)	Positive (right ureter)	Ileal conduit	5	15
6 M 69	BCG, Mitomycin	Multifocal	Ta N0	High grade	Yes	No	Normal	Negative	Ileal conduit	25	53
7 F 54	None	Multifocal	T1 N0	High grade	Yes	–	Low grade TCC (left)	Negative	Orthotopic neobladder	2	28

persistent positive urinary cytologies in two patients - one who was non-responsive and another who recurred after mitomycin. Two patients had solitary kidneys. The first had been submitted to laparoscopic NU before radical cystectomy for primary UUT TCC, and developed contralateral UUT recurrence in a non-functioning renal unit. The second developed bilateral, extensive disease, not amenable to conservative resection, and underwent open NU followed by contralateral laparoscopic NU.

Laparoscopic-assisted NU was performed in all patients using a transperitoneal approach. Pneumoperitoneum was achieved through a Veress needle placed lateral to the rectus abdominalis, away from the lower midline incision. The Visiport optical trocar (United States Surgical Corporation, USSC, Norwalk, CT, USA) was used for initial access to the abdomen. Local adhesions from previous surgery were carefully taken down with sharp dissection. The colon was then mobilized medially and the kidney removed in a standard laparoscopic fashion (6). In summary, a plane was created between the ureter and the aorta or the vena cava (for left and right-side NU respectively), and this was carried up to the renal hilum. The renal artery and vein were dissected and sequentially transected with the use of an endovascular GIA stapler (USSC, Norwalk, CT, USA). The adrenal gland was routinely spared by entering the Gerota's fascia and dissecting it off the upper pole of the kidney. The remaining of the dissection was carried outside Gerota's fascia. Following complete dissection of the kidney and upper ureter, dissection of the remaining ureter was carried down as far distally as possible. On the left side, the ureter was dissected to the area where the ureter traversed the mesentery of the sigmoid colon. On the right, the dissection usually approached the urinary diversion. A low abdominal incision (in the previous cystectomy incision site) was then made when the complexity of the dissection was beyond the limitations of a safe laparoscopic approach. The ureteroenteric anastomosis was identified and completely excised with a cuff of normal bowel mucosa. The urinary diversion was closed with running 3-0 polyglactin suture, and repositioned in its usual anatomic position. In the two cases with

solitary kidney, urinary diversion was removed en bloc with the kidney and ureter.

Operative results and outcomes of all patients treated by this technique were retrospectively reviewed and analyzed.

RESULTS

Five male and two female patients with a median age of 68 years (range 53 to 72 years) developed multifocal recurrent UUT TCC after treatment with radical cystectomy for bladder cancer. The features of these recurrences are shown in Table-3.

All patients required extensive lysis of adhesions due to the previous open surgery, and multiple prior ureteroscopies and biopsies. One of the patients could not have his entire kidney dissected laparoscopically due to a prior abdominal aortic aneurysm repair that resulted in a fibrotic reaction around the renal hilum. The midline incision was extended and the renal dissection was completed through the extended open incision.

No intraoperative complications from the laparoscopic procedure occurred. Two patients had intraoperative complications during the open stage of the procedure, due to the intense adjacent reactive process. The first had an inadvertent bowel injury, which was managed with segmental enterectomy. In the second patient, transection of the contralateral ureter was recognized intraoperatively, requiring reanastomosis to the ileal conduit.

All patients had delayed return to bowel function beyond three days. Other minor post-operative complications occurred in two patients. One had colonic pseudo-obstruction that resolved with conservative management, and the other presented with a superficial wound infection treated with intravenous antibiotics. Two other patients developed anticipated end-stage renal disease due to previous contralateral NU. They were started on hemodialysis and required longer hospitalizations due to instituting dialysis in the setting of no renal function.

The mean operative time was 305.6 minutes (range 220 to 360 minutes), and estimate blood loss

Table 3 – Clinical-pathological features of upper urinary tract recurrences after radical cystectomy.

Pt. N. Sex Age	Symptoms	Positive Diagnostic Studies	Side of Recurrence	Site of Recurrence	Previous Treatments for UUT TCC	Final Treatment	Pathological Stage	Pathological Grade	Margin Status
1 M 65	None	Urine cytology, ureteroscopy with biopsy	Left	Renal pelvis, distal ureter	None	Left lap-assisted NU	T3	High grade	Negative
2M 53	None	Urine cytology	Left	Renal pelvis	None	Left lap-assisted NU	Tis	–	Negative
3 F 68	Gross hematuria	Urine cytology, CT scan, ureteroscopy with biopsy	Left	Renal pelvis	None	Left lap-assisted NU	T2	High grade	Negative
4 M71	None	Urine cytology, retrograde Pyelogram, ureteroscopy with biopsy	Left	Renal pelvis, proximal ureter	None	Left lap-assisted NU	T3	High grade	Negative
5M 72	None	Urine cytology	Bilateral	Distal ureter (bilateral)	Mytomicin	Right lap-assisted NU, distal ureterectomy (left)	Tis	–	Positive for carcinoma in situ (bilateral)
6 M 69	Gross hematuria	Urine cytology, ureteroscopy with biopsy	Left	Renal pelvis, distal ureter	Right lap-assisted NU, distal ureterectomy, Percutaneous resection (left)	Left lap-assisted NU	T1	High grade	Positive for invasive carcinoma
7 F 54	Gross hematuria	Urine cytology, IVP, nephroscopy with biopsy	Bilateral	Entire UUT (bilateral)	Left Mid/distal ureterectomy, bilateral percutaneous resection, right open NU	Left lap-assisted NU	T3	High grade	Positive for carcinoma in situ (left)

was, in average, 180 mL (range 100 to 250 mL). Mean length of hospital stay was 10.8 days (range 5 to 25 days). Follow-up averaged 14.6 months (range 2 to 22 months), although two patients were lost to follow-up. The remaining five patients were regularly followed-up for more than 12 months. Table-4 gives an overview of the outcomes from each of the cases studied.

COMMENTS

TCC is a multifocal disease affecting the entire urothelium (7,8) and subsequent tumors may occur anywhere in the urinary tract after initial diagnosis (9). While primary UUT TCC is frequently followed by bladder recurrences, (7,10) and the cumulative incidence of UUT recurrence after bladder cancer is up to 28% in five years,(11) the incidence of UUT tumors after radical cystectomy is low (7-9). The incidence of post-cystectomy UUT TCC differs according to the stage of the bladder tumor. Patients submitted to radical cystectomy for superficial disease have a higher probability of developing UUT tumors than those with muscle-invasive disease (8). Other risk factors responsible for UUT recurrences in these

patients include histological grade, presence of distal ureteric carcinoma at cystectomy, associated CIS, multifocality, and involvement of the prostatic urethra (8,9,12).

The optimum method of surveillance of the UUT after cystectomy is questionable. Various regimens with annual or biannual imaging (IVU or CT), combined with urine cytology, have been reported (9). Since six (85.7%) of our patients had distal ureteral involvement by CIS or TCC, we adopted a more aggressive surveillance, similar to that for superficial bladder tumors, with urine cytology, imaging studies, and UUT endoscopy.

The role of urinary cytology in the diagnosis of UUT TCC is controversial, in particular for patients with intestinal diversions, because of the presence of small bowel cells (7). However, since most UUT TCC after cystectomy tends to be high grade, sensitivity is higher in these patients (9). Obtaining urine using ureteral catheterization further improves the diagnostic yield (13). IVU and CT scans increase the likelihood of early detection, and help in management decisions, but the key role in the diagnosis of recurrent UUT TCC is retrograde pyelography and ureteroscopy with biopsy, with a reported accuracy of 94% (13).

Table 4 – Oncological outcomes after laparoscopic-assisted NU for recurrent UUT TCC.

Pt. N. – Sex – Age	Recurrence	Local	Treatment	Follow-up	Status
1 – M – 65	No	–	–	3	No evidence of disease
2 – M – 53	No	–	–	20	No evidence of disease
3 – F – 68	Yes	Brain	Frameless stereotaxy	22	With disease
4 – M – 71	No	–	–	13	No evidence of disease
5 – M – 72	No	–	–	22	No evidence of disease
6 – M – 69	No	–	–	2	No evidence of disease
7 – F – 54	Yes	Pelvic	Chemo-therapy	20	With disease

The historic standard of care for high grade and stage UUT lesions has been open NU, with removal of a cuff of bladder around the ureteral orifice.(2-6,12-14) Several centers have replaced the open surgery for laparoscopic NU, given that it has well established advantages compared to the open approach, (2-6,8,14) and it is equally effective in terms of oncological outcome.(2-5,14) Following this trend, after performing over 80 laparoscopic NU at our department, we started performing laparoscopic-assisted NU for recurrent UUT TCC post-radical cystectomy in 2003. Surgical technique mirrors traditional open NU, including the removal of a cuff of bowel at the ureteroenteral anastomosis. All except one patient had the renal portion of the procedure successfully accomplished laparoscopically, and all surgeries were completed through the same previous incision performed for radical cystectomy, including the patient that required open conversion for marked hilar vessels fibrosis. In this patient, the incision was extended to the xiphoid process.

Mean operative time was long compared to standard NU but this was not due to the laparoscopic nephrectomy portion of the procedure but rather the complex dissection of the urinary diversion and necessity for complete removal of the ureter with a cuff of the bowel. In all cases, extensive and tedious lysis of adhesions was necessary to release the diversion and distal ureter from adjacent bowel. It is not surprising that delayed recovery of bowel function was seen in these patients, resulting in a lengthened hospital stay when compared to NU with no prior cystectomy. In addition, 2 patients had solitary kidneys removed and subsequently required postoperative dialysis, which made management and hospitalization more complex. These patients had failed prior attempts at organ sparing therapy.

The outcome of patients who develop UUT TCC after cystectomy is usually poor (1,7,12). So far, two of our patients presented recurrences, although the median follow-up is still limited. In addition, these patients are at higher risk of TCC in remaining sites due to the multifocal nature of their disease. Lifelong surveillance for recurrent disease in remaining urothelial surfaces and distant sites is necessary.

CONCLUSIONS

Our experience confirms that NU for UUT TCC after radical cystectomy is a complex procedure due to the altered anatomy and the presence of many adhesions. In the present series, a laparoscopic-assisted approach could be performed safely in properly selected cases but did not yield the usual benefits of decreased hospitalization seen with other laparoscopic renal procedures mainly due to patient co-morbidities and the delayed return to bowel function. We even still prefer this approach, as after many years of experience the majority of our surgeons regularly performing renal surgery feel more comfortable with the laparoscopic approach to the kidney. The distal ureter and bowel cuff, however, must still be extracted with open surgery. We recognize that advanced laparoscopic experience is required to achieve even comparable results to an open approach in this technically demanding procedure.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Radical cystectomy with extended lymph node dissection is the gold standard treatment for invasive and/or refractory superficial bladder cancer (1). Although upper tract recurrence after radical cystectomy has a low incidence at 2% to 4%, it is associated with poor prognosis, and a short survival

(2). The disease specific-survival of patients with upper tract transitional cell carcinoma (TCC) and previous bladder cancer is worse when compared to patients with no bladder tumor, suggesting more aggressive pattern when the pan-urothelial disease is present (3). Laparoscopic nephroureterectomy is

routinely used to treat upper tract TCC with low morbidity and complication rate, and similar oncological outcomes comparable to the open procedure (4).

The authors are to be commended for this series of 7 cases of laparoscopic-assisted nephroureterectomy in patients with previous cystectomy for bladder TCC. In the cystectomy specimen, all patients had bladder carcinoma in situ (CIS), with 6 presenting ureteral CIS, and 4 of them presenting positive margin. These factors may increase the recurrence rate. During the follow-up, 3 patients presented with gross hematuria, but all had positive urinary cytology. A recent study by Raj et al. (2) showed the relevance of urinary cytology after radical cystectomy demonstrating not only the higher risk of recurrence but also the shorter survival; suggesting the need for closer follow-up and the potential for early adjuvant therapies.

The morbidity of the procedure in this group of patients was expectedly higher when compared to standard laparoscopic nephroureterectomy, with longer operative time, hospital stay, and bowel function recovery. One open conversion, one bowel and one intraoperative ureteral injury were reported in the study, with 40% positive margins in the pathological exam.

With the intention of minimizing the morbidity of the procedure, the retroperitoneal approach to the nephrectomy part of the procedure may be helpful in avoiding intra-abdominal adhesions due to the previous cystectomy site; the distal ureterectomy part of the procedure would be performed as described by the authors. These are surgically challenging cases in often unhealthy individuals.

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Long-Term Results of Simple Enucleation for the Treatment of Small Renal Cell Carcinoma

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ABSTRACT

Objective: We have analyzed our institutional experience with simple enucleation for the treatment of small renal tumors for elective indications.

Materials and Methods: A total of 30 patients underwent elective nephron-sparing surgery (NSS) from May 1997 to January 2001. All patients underwent NSS by means of enucleation. The tumor bed was coagulated carefully for haemostatic and partly for oncological reasons. Median follow-up was 71 months (range: 49-91 months).

Results: Pathological review according to the 2002 TNM classification showed that 70 % (21 of 30) of tumors were pT1a, 26.7 % (8 of 30) pT1b and 3.3 % (1 of 30) pT3a. Median tumor size was 3.7 cm. (range: 3.0 - 5.5 cm). There was no perioperative mortality (within the first 30 days). Bleeding had not been recorded during perioperative period. Urinary leakage was observed in 1 patient (3.3%). No case of local recurrence was observed. Five and 7-year cumulative survival was 96.6% and 93.3%, respectively. Five and 7-year cancer specific survival was 100% and 96.5%, respectively.

Conclusions: Simple tumor enucleation is a safe and acceptable approach for elective NSS. It provides excellent long-term progression-free and cancer specific survival rates, and is not associated with an increased risk of local recurrence compared to partial nephrectomy.

Key words: renal cell carcinoma; surgery; postoperative complications; survival rate

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INTRODUCTION

Nephron sparing surgery (NSS) was initially used in the treatment of renal cell carcinoma (RCC) only for absolute and relative indications (1,2). The widespread use of modern radiological modalities substantially changed clinical presentation of renal tumors in recent decades. Currently, more than one-half of all patients with surgically resectable renal tumors are detected incidentally (2,3). In the patients with normal contralateral kidney, NSS became a standard method of treatment. Several trials have shown

survival rates similar to those obtained with radical surgery for low stage, low-grade lesions with less than 4 cm of size (2,4-6).

Local recurrence is the major drawback of NSS mostly due to incomplete resection of the primary tumor. Thus, tumor excision without leaving residual malignant tissue in the renal remnant is very important. However, the optimal margin that should be resected during NSS is still controversial. The recommended minimal size of resected parenchyma in NSS varies from investigator to investigator and includes 0.5 cm (5), 1 cm (6), "a rim" of normal ap-

pearing parenchyma (7), and even simple enucleation (6,8,9). Several recent studies have shown that a minimal layer of healthy parenchyma is quite enough without compromising oncological outcome. The simple enucleation technique, which was previously described as treatment of choice for benign kidney tumors like angiomyolipoma, was also used for the treatment of small RCC by some authors. To our knowledge, only few studies have been conducted during the last decade assessing efficacy of enucleation in RCC (6,8,9). In the present study, we evaluated retrospectively 30 cases of NSS performed at our institution for elective indications.

MATERIALS AND METHODS

Thirty patients underwent NSS for elective indications From May 1997 to January 2001 (Table-1). There were 19 (63.3%) males, and 11 (36.7%)

Table 1 – Clinicopathological characteristics of 30 patients.

Pte. Age at Surgery (years)	
Median (range)	49 (37-68)
Pathological tumor size (cm)	
Median (range)	3.7 (3.0 - 5.5)
Gender	
N Male (%)	19 (63.3%)
N Female (%)	11 (36.7%)
N Tumors incidentally discovered (%)	27 (90%)
N 2003 tumor stage (%)	
pT1a	21 (70%)
pT1b	8 (26.7 %)
pT3a	1 (3.3%)
N Nuclear grade (%)	
G1	12 (40%)
G2	15 (50%)
G3	3 (10%)
N Histological subtype (%)	
Clear cell	22 (73.3%)
Papillary	5 (16.7%)
Chromophobe	2 (6.7%)
Cystic RCC	1 (3.3%)
N Disease progression (%)	1 (3.3%)
Median follow-up in months (range)	71 (49-91)

females. The median age was 49 years (range: 37 - 68 years). Left side tumor was detected in 18 (60%) cases and right side in 12 (40%) cases. The tumor was in the upper pole in 11 cases (36.7%), mid kidney in 7 (23.3 %) and lower pole in 12 (40%). All tumors were located peripherally (defined as peripherally located and enveloped by cortical parenchyma, without extension into the renal sinus). At diagnosis 27 (90%) tumors were detected incidentally, whilst 3 (10 %) were associated with microscopic hematuria. All patients were evaluated carefully preoperatively to exclude the presence of distant metastases. Preoperative evaluation included ultrasonography of the kidney, CT of the abdomen and chest X-ray in all patients. Renal function was assessed by means of serum creatinine level.

All patients were operated through extraperitoneal, extrapleural incision above the 12th rib. The kidney was completely mobilized to exclude the presence of satellite tumors. Peritumoral fat was left in situ. A sharp incision on the renal capsule was performed 2 to 3 mm away from the tumor margin. The renal pedicle was completely isolated and the renal artery was clamped just before beginning the incision on the renal capsule. The venous clamping was not used in any case. To reduce the outcomes of renal ischemia vigorous hydration, mannitol infusion before the arterial clamping and renal hypothermia with ice was adopted in all cases. Tumors were enucleated without a layer of normal parenchyma. During the enucleation, a cleavage plane between pseudocapsule and normal parenchyma was created by means of scissors, without blunt finger dissection. All tumors presented a real pseudocapsule, which facilitated the enucleation. Tumor bed was inspected very carefully. Intraoperative frozen section of tumor bed was performed routinely in all cases. The results of frozen section were negative in all cases. The data of the patients who underwent nephrectomy due to positive margins found during frozen sections, were not included in the study. The visible bleeding vessels and opened calices were closed using running sutures. Finally, tumor bed was coagulated carefully for haemostatic and partly for oncological reasons. The coagulation was performed by means of diathermy spray coagulation. We did not wait for the

intraoperative frozen section under renal ischemia and went forward with the next steps of the operation. The parenchymal defect was closed using absorbable interrupted sutures. In case of large capsular defect, it was covered with free peritoneal graft.

Pathological tumor staging was performed according to the 2002 TNM staging system (10) and nuclear grade was assigned according to Fuhrman's grading system (11). The removed tumor specimen was always inspected by pathologists and the surgical margins were inked.

The patients were followed with renal functional tests, chest x-ray, abdominal ultrasound or CT scan every 3 months during the first year, once in 6 months for the next two years and annually thereafter. In terms of statistical analysis, the probability of cumulative and cancer-specific survival was estimated by the Kaplan-Meier method using the whole number of events.

RESULTS

Twenty one out of 30 tumors were pT1a (70%), 8 were pT1b (26.7%) and 1 was pT3a (3.3%). The median tumor size was 3.7 cm. (range: 3.0 - 5.5 cm). Final pathological evaluation did not reveal any case of tumor extension out of the inked area of the surgical specimens. Grade 1 was diagnosed in 12 (40%) cases, Grade 2 in 15 (50%) cases and Grade 3 in 3 (10%) cases. Pathological T3a case was confirmed by the microinvasion of the surrounding perirenal fat. Histological classification revealed 22 clear cell (73.3%), 5 papillary (16.7%), 2 chromophobe (6.7%) and 1 cystic (3.3%) RCC.

The median time of renal ischemia was 22 minutes (range: 18-35min.). No perioperative mortality and/or serious general complications (myocardial infarction, deep venous thrombosis etc) were observed. No wound infection was observed during the early postoperative period. Bleeding had not been recorded during early postoperative (within the first 30 days) period. Urinary leakage was observed in 1 patient (3.3%) and patient required double-J stenting. Median hospital stay was 6 days (range 4 - 15). The median follow-up was 71 months (range: 49 - 91

months). No case of local recurrence was observed. Renal functions were stable in all patients during follow-up period. Renal function remained stable in all patients with a median postoperative creatinine level of 0.9 mg/dL (range: 0.7 - 1.4 mg/dL).

One patient with pT1b, G3 disease developed osseous metastases and died 81 months postoperatively. The tumor size in this patient was 45 mm. One patient died for kidney unrelated cancer reasons without evidence of tumor recurrence.

The remaining 28 patients are alive without evidence of disease recurrence at the last checkup. Five and 7-year cumulative survival was 96.6% and 93.3%, respectively (Figure-1). Five and 7-year cancer specific survival was 100% and 96.5%, respectively (Figure-2).

COMMENTS

Local recurrence is the major drawback of NSS mostly due to incomplete resection of the primary tumor, occult multicentric disease, or the development of new primary or metastatic cancer in the

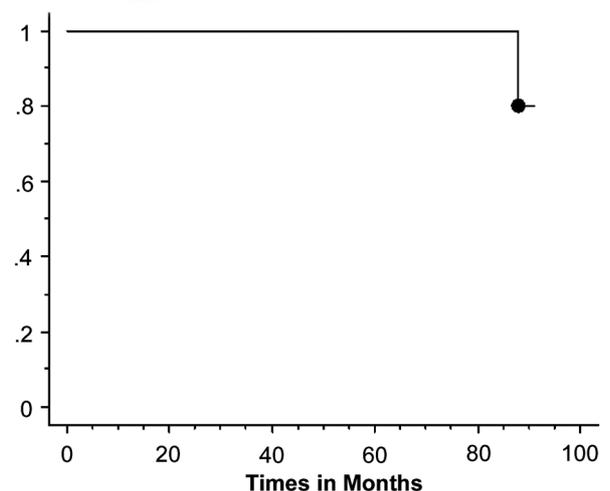


Figure 1 – Cancer-specific survival rate in patients undergoing nephron-sparing surgery by simple enucleation.

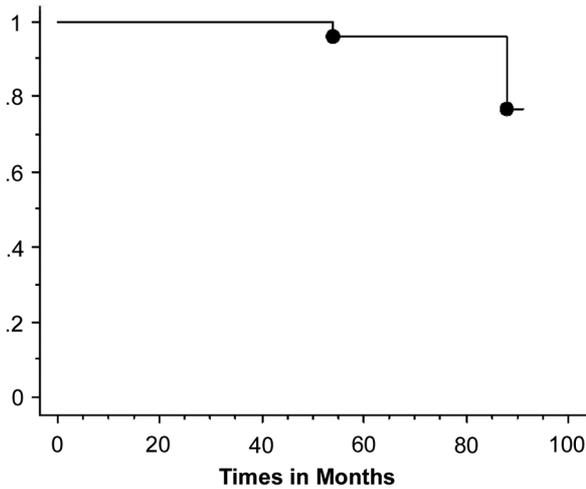


Figure 2 – Cumulative survival rate in patients undergoing nephron-sparing surgery by simple enucleation.

renal remnant. Uzzo & Novick reviewed more than 1,800 cases of NSS in several large series and showed that the true biological significance of multicentric renal tumors and its implications for NSS remain to be completely elucidated (2). The major practical concern is to avoid the risk of positive margins after NSS. It was widely accepted that tumor should be excised with a piece of normal parenchyma however the minimal size of the parenchyma has been the subject of controversies for a long time. In the 1950s Vermooten first suggested that peripheral renal neoplasms could be excised leaving a margin of normal parenchyma around the tumor. He suggested the margin of at least 1 cm (12). For many years there was an agreement that 1 cm margin of normal parenchyma was the safest way to prevent local recurrence after NSS. For a variety of other tumors (e.g. colon cancer, breast cancer, melanoma, sarcoma) 1-2 cm margin is recommended to minimize the risk of local recurrence, which seems suitable due to the infiltrative growth of these tumors. RCC tends to compress normal parenchyma and forms a pseudocapsule around the tumor, thus the necessity of 1 cm resection margin seems to be overestimated. However, the rationale to perform NSS in patients with normal renal function and contralateral kidney is to preserve the renal parenchyma as much as possible and reduce the likelihood of deterioration of the renal function.

In recent years, the necessity of a conventional 1 cm margin has been revised substantially. Li et al. evaluated prospectively 82 RCC of 4 cm or less resected by radical nephrectomy. The maximal extrapseudocapsule cancer extension was measured. Positive cancer lesion beyond the pseudocapsule was detected in 19.5 % of cases with an average distance of 0.5 mm from the primary tumor. The authors considered that when partial nephrectomy is performed for RCC of 4 cm or less a 1 cm margin might be too much while enucleation alone may be associated with a significant risk of incomplete excision. Five mm margin could be enough to prevent possible local recurrences (13). Moreover, Pipper et al. showed that even 1 mm margin of normal tissue around the tumor is sufficient to prevent local recurrences. In these series by Piper et al., among the tumors resected with less than 1 mm margins no local recurrences were observed (14). Castilla et al. did not reveal any correlation between the size of the resection margin and disease progression (15). Sutharland et al. mentioned that the size of the margin was irrelevant as long as the surgical bed was free of residual tumor. Therefore, only a minimal margin of normal renal parenchyma must be removed during NSS for low stage RCC (16). Puppo et al. assessed safety and effectiveness of the excision of small renal cancer surrounded by a minimal layer of grossly normal parenchyma. None of the patients in these series had positive surgical margins nor had a local recurrence after surgery at median follow-up of 59 months (7). According to the authors, the mean and median shortest distances from the tumor to inked healthy tissue were 2.4 mm and 1.9 mm respectively. Regrettably, the authors did not provide data about the range of shortest distances from tumor to the inked healthy tissue. Therefore, we do not know whether or not in some of its enucleo-resections the tumor was resected without a rim of normal parenchyma.

All these reports suggest that incidentally detected small renal tumors (less than 4 cm) have a benign behavior and the conventional 1 cm resection margin of normal parenchyma could be abandoned without any significant oncological risk. On the background of these studies reevaluation of the efficacy of simple enucleation in the treatment of RCC seems reasonable. Few studies in the late 1980s and early

1990s investigated the efficacy of simple enucleation for the treatment of small RCC and showed 5-year survival rates similar to partial nephrectomy in a selected group of patients. Tumor enucleation has been shown to be effective in providing intermediate cancer-free intervals in patients with peripheral lesions (17,18). However, other authors reported increasing as compared with the partial nephrectomy incidence of local recurrences after simple enucleation (19,20). We think, this can be explained by the blunt finger enucleation technique instead of sharp dissection and improper patient selection. Lerner et al. showed that cause-specific survival was not significantly different after enucleation, in situ partial nephrectomy, or radical nephrectomy in patients with a solitary, ≤ 4 cm tumors. They suggested that tumor enucleation using sharp dissection guided by the intraoperative frozen section analysis virtually eliminates the chance for incomplete primary tumor removal (6). Lapini et al. assessed the feasibility and effectiveness of simple enucleation for the elective treatment of RCC. They presented a retrospective study, which is based on the review of 107 clinical cases. Three patients had disease progression: 2 had local, 1 isolated and 1 associated recurrence with distant metastases. The authors show that simple tumor enucleation is a useful and acceptable approach for elective NSS (9). One of the major concern related with an enucleation during RCC is a possible microscopic tumor penetration of the pseudocapsule that surrounds the neoplasm but as it was reported by Li et al. (13) the average distance of tumor invasion beyond pseudocapsule is only 0.5 mm, while in our patients tumor enucleation is always followed by coagulation of the enucleation bed, which provides approximately 1 mm thickness of parenchymal coagulation and therefore prevents risk of local recurrence. Despite of some similarity with enucleo-resection we consider that enucleation with a coagulation of the tumor bed is different technique because it leads to the necrosis of 1 mm of healthy parenchyma while during the enucleo-resection the mean size of "sacrificed" parenchyma is about of 2.4 mm (7).

To our knowledge, there is no definite evidence of theoretical advantage of true partial nephrectomy over enucleation today. In our study we did not observe local recurrence during a long follow-up

period. We had cancer specific and recurrence-free survival rates comparable to other published series (2,4,5). Another important concern in NSS is the possibility of early postoperative complications. The rate of acute or delayed hemorrhage ranges between 1.3 - 7.9% in published series (2). We did not observe these complications in our study. Urinary fistula is one of the most common complication after NSS with a reported mean rate of 6.5% (2). We consider that a minimal rate of morbidity in our study was caused partly due to strict patient selection and partly due to the technique of enucleation.

Finally, the aim of our study was not to show any advantages of simple enucleation over enucleo-resection or wedge resection, but to try to demonstrate that oncological results of simple enucleation are at least not inferior comparing to other forms of NSS. At the same time enucleation leads to lower complication rate with maximal preservation of renal parenchyma.

CONCLUSIONS

The results of our study show that simple enucleation is an effective and acceptable method of operative treatment of RCC, which does not compromise the oncological outcome providing excellent long-term progression-free and cancer specific survival. It provides maximal preservation of renal parenchyma and lower incidence of postoperative complications. Larger and long-term studies are needed to prove improvement of the renal function after simple enucleation as compared to other NSS operations.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Pertia & Managadze performed a sharp dissection of small to medium sized renal tumors using a standard open technique in 30 patients. They termed their procedure simple enucleation although I had the impression that enucleation was performed with a finger to define by tactile means the true or pseudocapsule between the tumor and the normal parenchyma. They obtained a frozen section of the base however; they did not wait for the result to close the defect. They state that the results were always negative thus; they did not perform a total nephrectomy in any case because of a positive margin. Importantly although their series is relatively small, there were very few complications and the one leak was readily corrected with a stent. Although not stated it is likely all patients had a normal contralateral kidney and thus not surprisingly the renal function was not altered in any patient.

I perform the procedure in virtually an identical fashion as described by the authors. I believe an open flank approach for a partial nephrectomy for larger renal masses is a very safe procedure. The surgeon has excellent control of the vasculature and there is minimal bleeding. The new hemostatic agents are a real advance and provide an additional means to ensure hemostasis after careful suturing of small vessels before the capsular closure with gelfoam pledgets.

There is a word of caution however. Despite the nice results presented here given enough cases there might be the occasional patient who has a positive margin on a permanent section and the surgeon and his patient have the difficult decision of whether to return to the operating room (which usually means a nephrectomy) or monitor the kidney with lifelong imaging under the constant fear of a recurrence. It is always more comfortable to have that extra little bit of normal tissue around the tumor with a pathology report confirming that none of this tissue has any tumor. Do I always follow this rule? Not always but I feel more comfortable when I do. Once again, with appropriate vascular control and the new agents to aid in hemostasis the morbidity is not increased with this extra bit of caution. Given the “benign” behavior of most of these small tumors, one is not likely to tell a difference between no additional margin and a few mm of additional parenchyma. Some of our patients as in this series are young and in the case of a final permanent margin in such a patient, it will require many years to determine whether tumor was indeed left and the implications.

Finally, Webster’s dictionary defines enucleate as “to remove without cutting in to”. Thus, the authors must come up with another term since their dissection is sharp and they are cutting the parenchyma to remove the tumor.

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EDITORIAL COMMENT

Although radical nephrectomy (RN), as described by Robson et al. has been the gold standard for patients with renal cell carcinoma (RCC) for many

decades, there is a trend towards nephron sparing surgery – NSS (1,2). This evolution is the result of improved surgical technique, standardized staging,

advanced radiological imaging and downward migration toward the diagnoses of asymptomatic, incidental, smaller, lower-stage lesions and the associated low rate of adrenal and lymph node metastases (3). NSS for tumors less than 4 cm (T1a) is at present widely accepted even for elective indications, while the use of NSS for patients with larger T1 tumors (T1b) is much more controversial (4). Although oncological results appear to be equal for NSS and RN for small tumors and the advantage is renal function is evident, NSS is still largely underused, as shown in a recent analysis (5). A margin of 1 cm of normal appearing parenchyma was long considered the standard in NSS (6). However, wide margins may compromise the residual renal function. The optimal resection margin is still debated because satellite lesions can be found more than 1.0 cm beyond the primary tumor (7). Sutherland et al. investigated the effects of surgical margin on recurrence. They concluded that the margin width is irrelevant if the tumor is completely resected and that it was not correlated with disease progression. The oncological result was independent of the margin width (8). Lapini et al. even showed that simple enucleation is a safe and acceptable approach (9). The present paper by Pertia et al. nicely provides additional evidence in favor of simple tumor enucleation in cT1a and cT1b RCC. In their limited series of 30 patients, complication rate was very low, with only 1 urinary leakage, requiring a double-J stent, and no hemorrhagic complications. The median follow-up was a substantial 71 months. Five- and 7-year cancer specific survival was impressive at 100% and 96.5% respectively. Of note is that they routinely performed frozen sections of the tumor bed, and patients who presented with a positive section margin underwent subsequent radical nephrectomy and were excluded from the analysis. This might have biased the results towards a more favorable outcome. It would have been interesting to know exactly how many patients were in this case. Furthermore, all resection beds were routinely coagulated, using diathermy spray coagulation. This is important, as coagulation will destroy another 1 to 2mm rim of parenchyma. Lapini et al. similarly used diathermy spray coagulation or argon beam laser to the tumor bed. In our opinion, this might explain why

enucleation provides the same results as nucleoresection, where a minimal rim of healthy tissue is resected together with the tumor (9).

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Carcinoma of the Renal Pelvis and Ureter

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ABSTRACT

Objective: To assess the occurrence of upper urinary tract urothelial tumors (UUTT) in Brazil.

Materials and Methods: We performed a clinical and histopathologic study of 33 patients who were diagnosed with a malignant neoplasm in the renal pelvis or ureter in the period of 1994 to 2004, in a single institution.

Results: Among the patients with upper urinary tract carcinoma, 70% were males and 30% females, with mean age of 65 ± 16 years (ranging from 31 to 91 years). Nineteen patients presented renal pelvis tumor (58%), 9 ureteral tumor (27%) and 5 synchronic pelvic and ureteral tumors (15%). Renal pelvis tumors represented 2.8% of all the urothelial neoplasms, and 11.4% of all renal neoplasms treated in the same period. Ureteral tumors represented 1.6% of all the urothelial malignancies surgically managed in these 11 years. Tobacco smoking was the most common risk factor, and analgesic abuse was not reported by those patients. Most carcinomas were high-grade and muscle-invasive. Mean time to diagnosis was 7 months, being hematuria the most common symptom.

Conclusions: A high association was also found between UUTT and bladder urothelial carcinoma. UUTT were mostly seen in men in their seventies and related to a high overall and cancer-related mortality rate.

The overall disease-specific survival was 40%, much lower than found in most of the reported series.

Key words: kidney; ureter; neoplasms; transitional cell; epidemiology; Brazil

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INTRODUCTION

Upper urinary tract tumors involving the renal pelvis and ureter are relatively uncommon. The great majority of these are epithelial, 80% are malignant and 90% are urothelial carcinomas. Renal pelvis tumors account for approximately 7 to 10% of all renal tumors and about 5% of all urothelial tumors (1-9). Ureteral tumors are even more uncommon, occurring in one fourth of the incidence of renal pelvis tumors (1,10).

Many factors contribute to the development of upper urinary tract urothelial tumors (UUTT), some

of them similar to bladder cancer associated factors, and the most common of these are tobacco smoking and analgesics abuse, particularly phenacetin (2,3,5,11-13). Other risk factors include papillary necrosis, chronic urinary infections, renal calculi, occupational exposure, Balkan nephropathy, thorium containing radiologic contrast medium and family associated cancer syndromes (2,3,5,12-14). The behavior of the UUTT is also similar to the bladder urothelial carcinoma, presenting high recurrence rates and usually is multicentric (2,3,9).

In the bladder, however most urothelial carcinomas are superficial at diagnosis (3,5). In these

cases, organ-sparing procedures are the treatment option. For UUTT, nephroureterectomy with bladder cuff removal has been the conventional treatment. More recently, with the introduction of endourological techniques, approaches that are more conservative have been advocated in selecting patients in an effort to salvage kidneys. However, different from bladder carcinoma, radical surgery is more often used in UUTT cases, as the diagnosis is commonly made at advanced stages and management by conservative measures is problematic (3).

Among the North-American population, there has been an increase in women affected, and it tends to occur at an older age (3,5,15). Large demographic studies have been undertaken in several countries (2,4,6-9,15-19) but to our knowledge, there is no study analyzing data about UUTT in the Brazilian population.

The aim of the present study is to assess the occurrence of UUTT in 33 patients who underwent surgery from 1994 to 2004 in a single institution.

MATERIALS AND METHODS

Surgical pathology files of all patients who underwent surgery for primary UUTT at the Division of Urology of the authors' institution from 1994 to 2004 have been retrospectively reviewed (33 subjects).

Macroscopic data were obtained from the pathological reports. The hematoxylin and eosin stained slides were reviewed by one pathologist with special expertise in the field of uropathology (MGC). Slides on each case were collected and reclassified using the criteria of the 2004 WHO grading system (5). All tumors were restaged based on TNM (tumor node metastasis) staging system, 2002 (20). All urothelial and renal tumors surgically treated during the same period in the referred institution were also revised in order to calculate disease-related prevalence.

Further data were obtained from the hospital database and patients notes, including patients' demographics, anatomical location of the tumor, surgery outcomes, disease recurrence, specific survival and overall survival. Contact was established with

the patient and/or family whenever possible, and the district death registry was consulted for the remaining cases.

Disease-specific survival was assessed by the Kaplan-Meier method and compared by the Log-Rang test.

The institutional medical ethics committee approved the present study.

RESULTS

Among patients with UUTT, 70% were males and 30% females, with a mean age of 65 ± 16 years (ranging from 31 to 91 years). Ninety-one per cent of the patients were white and 9% black. The left side was affected in 61% of the cases and the right side in 39% (Table-1).

Nineteen patients had only renal pelvis tumor (58%), 9 had ureteral tumor (27%) and 5 had both pelvic and ureteral tumors (15%). Renal pelvis urothelial carcinomas represented 2.8% of all the urothelial neoplasms surgically treated in our institution during this period, and 11.4% of all renal tumors. Ureteral tumors represented 1.6% of all the urothelial malignancies surgically managed. In 50% of the patients the distal ureter was affected, middle and proximal ureter were respectively affected in 29% and 21% of the patients.

Association with bladder cancer was present in 30% of the patients. In 17% of them, there had been a previously treated bladder cancer (mean of 4 years previously) and in 23%, there had been a synchronous bladder neoplasm. In 15% of the cases, there had been synchronous ureteral and pelvic neoplasm

Table 1 – Clinical features of upper urinary tract urothelial tumors.

Feature	Value
Male / Female	70% / 30%
Mean age (years)	65 ± 15
Right / Left	39% / 61%
Bilateral	3%
Mean follow-up (range)	7 ± 3 (1-11 years)

and in 3% of the patients, bilateral disease had been found.

Hematuria was the most common symptom, seen in 45% of the patients. Other presenting manifestations included anemia (43%), flank pain (30%), weight loss (27%), fever (17%) pyelonephritis (17%) and palpable mass (10%). Diagnosis due to incidental finding during follow-up of previous urothelial carcinoma occurred in 10% of the patients. In the cases that weight loss, the mean loss observed was 5 Kg.

Mean duration of symptoms prior to diagnosis was 6.9 ± 4.3 months. Initial diagnosis was UUTT in 85% of the cases. In 6% of the cases, renal cancer was suspected and in 9% of the cases, the surgery was undertaken with the diagnosis of pyonephrosis, and the presence of cancer was confirmed during pathologic exam.

Regarding risk factors, tobacco smoking was referred by 66% of the patients and 33% had recurrent urinary tract infections or calculi. In one patient there was an hereditary nonpolyposis colorectal cancer syndrome associated (3%). Analgesic abuse was not referred to as risk factor in any patient.

Surgical treatment consisted of radical nephroureterectomy and bladder cuff removal in 65% of the patients; in 6% radical cystectomy was also performed; in 16% only distal ureterectomy and re-implant was performed, and in 13% only nephrectomy. Radiation therapy and chemotherapy were respectively combined in 6% and 12% of the cases.

Pathological exam demonstrated high-grade malignancies in 58% of the renal pelvis neoplasms and in 86% of the ureteral neoplasms. Regarding renal pelvis neoplasms, pT3 was the most common

stage, observed in 37% of the patients; pTa was observed in 29%, pT1 in 12%, pT2 in 12% and pT4 in 8% (Table-2). In ureteral neoplasms, pTa was the most common stage, observed in 28% of the cases. Stages pTis, pT1, pT2, pT3 and pT4 occurred respectively in 7%, 14%, 21%, 14% and 14% of the cases (Table-2). In 93.9% of the patients there was an urothelial tumor, and in 6.1% a squamous cell carcinoma. Squamous cell differentiation was observed in 9.7% of the urothelial carcinomas (3 cases). In all the cases with squamous cell differentiation, pathological stage was pT3, and for pure squamous cell carcinomas, one had a pT3 stage and the other a pT4. All the patients with squamous cell differentiation or squamous cell carcinoma had renal calculi and/or infection associated. In terms of lymph node status, 85% of the tumors were at NX, 6% at N0 and 9% at N1-3.

During follow-up (mean 7 ± 3 years, ranging from 1-11 years), 10% were alive, 30% died due to other causes, 5% died due to surgical complications and 55% died due to the malignancy. Three patients presented bladder cancer (treated endoscopically) and one patient that had a previous renal pelvis neoplasm underwent a contra-lateral distal ureterectomy 2 years later due to UUTT. Adequate follow-up was possible in 61% of the patients.

Disease-specific survival was not related to tumor grade ($p = 0.31$) neither to pathologic stage ($p = 0.51$) in the present series.

COMMENTS

In the present series, UUTT prevalence related to renal and bladder cancer was similar to that

Table 2 – Distribution of renal pelvis and ureteral tumors according to histologic grade and stage.

		Ta	Tis	T1	T2	T3	T4	Total
Renal pelvis	LG	7 (29%)	0	1 (4%)	1 (4%)	1 (4%)	0	10 (43%)
	HG	0	0	2 (8%)	2 (8%)	8 (33%)	2 (8%)	14 (57%)
Ureter	LG	2 (14%)	0	0	0	0	0	2 (14%)
	HG	2 (14%)	1 (7%)	2 (14%)	3 (21%)	2 (14%)	2 (14%)	12 (84%)

LG = low-grade; HG = high-grade.

previously reported in other studies (1,2,21). The anatomical location of UUTT in the present study conforms to that previously described, with almost twice as many pelvicalyceal as ureteric tumors (22). Ureteric tumors were also more common in the distal third, followed by the middle and proximal portions of the ureter, as reported in other series (22). The incidence of bilateral synchronous tumors was similar to other series (1,2).

UUTT has also been found to be primarily a disease of white individuals (91% of the cases), and mostly affecting elderly men (15). The demographic characteristics of our patients showed a peak incidence in the seventh decade of life and male-to-female ratio of 2.3:1. This is different from the lower tract disease in which the male-to-female ratio is 3 to 4:1 (3).

In the American population, Munoz et al. observed that patients with UUTT are being diagnosed at an older age, and a higher proportion of female and nonwhite individuals have been diagnosed. In our patients, such variation has not been noticed. Even though the number of patients is limited, age, ethnics and gender characteristics of the patients with UUTT remained the same during the last decade (15).

According to the WHO 2004 grading system, tumors are grading as papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade and high-grade carcinomas. There were few studies that used this system (2-4,18,19). We did not identify any PUNLMP, similarly to Olgac et al. It seems that differently from what occurs in the bladder, PUNLMP occur less frequently in upper urinary tract (19). In the present study, 86% of ureteral carcinoma and 58% of renal pelvis carcinoma were high-grade. These findings are similar to others investigators' data (3,6,7,9,17-19,23), confirming that most of the patients treated for UUTT present a high-grade disease.

Squamous cell carcinoma has accounted for 6.1% of the UUTT, close to previously reported in other series (4,24,25). Also, as reported by Blacher et al. in our patients all the squamous cell carcinomas and the urothelial carcinoma with squamous cell differentiation occurred within the renal pelvis, and all of them were high grade and high stage diseases with extensive invasion of the renal parenchyma. All were

in pathological stage pT3 or pT4 and had an unfavorable prognosis (25). As previously reported, all the cases were associated to calculi, chronic infection and squamous metaplasia of the neighboring epithelium (4).

In 64% of the cases, muscle-invasive disease was found, confirming the fact that unlike urothelial carcinomas of the bladder, UUTT should therefore be regarded as an aggressive, high-grade cancer, unless proven otherwise (3,26). In the reported cases however, muscle-invasive disease was more frequent than observed in other large series, with pT2 stage or higher occurring in 42-49% of the UUTT (3,8,18,19).

In our study, 13 patients (39%) had multifocal disease at presentation. Of these, one had bilateral ureteral tumor, 5 had both pelvic and ureteral tumor, 3 had pelvic and bladder tumor, 3 had ureteral and bladder tumor and 1 had carcinoma in the pelvis, ureter and bladder. The multicentric characteristic of urothelial carcinomas may be explained by several theories, but the better accepted is the so-called field effect, suggesting that the entire urothelial surface has undergone a neoplastic change (2).

Mean time from the beginning of symptoms to diagnosis was 7 months, being hematuria the most common symptom. Even though good screening programs are not available for such tumors, adequate widespread information could lower the stage at diagnosis. In the present study, a close association was found between UUTT and bladder urothelial cell carcinoma. Diagnosis and follow up of these bladder tumors allowed an earlier diagnosis of 10% of upper tract carcinomas.

Long-term phenacetin abuse is a commonly reported risk factor for UUTT (12). However, in the present study it was not found to be a significant risk factor. Maybe the greater popularity of dipirone instead of phenacetin among Brazilians may explain this finding (27). Concerning risk factors, tobacco smoking, renal calculi and chronic infection were mostly observed.

Currently UUTT have been managed conservatively under certain circumstances, provided they are superficial tumors, with low grade of differentiation and completely removed endoscopically (28). The patient must also be strictly and regularly fol-

lowed (28). However, in patients studied, such criteria have not been fulfilled in any of the cases. In most of them, there were bulky high stage and high-grade lesions.

Overall 5-year disease-specific survival was 40%, much lower than most of the reported series, which varies from 67% to 75% (15,29,30). As stated previously, a high prevalence of muscle-invasive disease and a high stage at diagnosis was observed in these patients. As pathological stage is one of the most important prognosis predictor, a poorer survival would in fact be expected for the studied population (9,18).

When analyzing disease-specific survival, neither tumor grade nor stage was significant risk factors in the present series. However, the poor follow-up of these patients, associated to the limited number of patients could explain this observation.

In conclusion, the studied population showed prevalence of UUTT related to other urothelial and renal neoplasms similar to the ones observed in other studies. UUTT was mostly diagnosed in men in the seventh decade of life, and tobacco consumption has been the major risk factor for UUTT in the present population. UUTT was associated to a high overall and cancer-related mortality rate.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors report a study of the initial presentation of upper urinary tract urothelial tumors. The findings of the present study are coincident with the ones found in literature where those tumors are infre-

quent, representing less than 5% of urothelial tumors. It is highlighted that the main risk factors were tobacco smoking (66%) and recurrent infections (33%). The other risk factors described in literature (phen-

acetin, nephropathy by Chinese herbs, occupational factors, nephropathy of the Balkans) were not observed here due to population differences.

It is also mentioned that the presence of a squamous component confers more aggressiveness and worsens the patient's prognostic.

It is important to highlight the high incidence of bladder neoplasia associated to upper tract tumors, requiring close watch to it during the patient's follow-up period.

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EDITORIAL COMMENT

The authors report basic data and outcome for 33 patients with upper urinary tract tumors treated in a hospital in Brazil. Most patients had high-grade tumors and 21 out of 33 had invasive tumors. The disease-specific survival rate was 40%. The data are consistent with other reports from Europe and North America. Patients with organ-confined tumors (stages Ta/T1/T2) have a good prognosis, patients with non-organ-confined disease (stage T3/T4) have a very poor prognosis, and this has not changed much during the last 30 years.

So what is new in the treatment of upper tract tumors? Laparoscopic nephroureterectomy is a technically difficult procedure and may result in a faster

recovery but will not influence the long-term prognosis. Endoscopic surgery (ureteroscopy or percutaneous surgery) may of course be excellent for patients who have small-sized low-grade tumors. Such tumors are, however, rare and have a disease-specific survival close to 100% when treated with open surgery.

The low number of patients with renal pelvic and ureteral carcinoma treated at each center is one obstacle to improvement of the prognosis but with cooperation, prospective randomized studies are still possible. It would be of interest to evaluate whether preoperative chemotherapy can improve the poor prognosis among patients with stage pT3 renal pelvic carcinoma.

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EDITORIAL COMMENT

Korkes and associates describe their retrospective, single institution study on upper tract urothelial tumors (UUTT) in 33 contemporary patients. The authors report that in long-term follow-up the disease-specific was only 40%, which highlights the aggressive nature of UUTT. Not

unsurprisingly, 66% of the patients in the study were tobacco users.

Most importantly, the authors note that the average duration of symptoms prior to diagnosis was 7 months. It is during this extended period of time that curable disease may be advancing. Other studies

have also demonstrated a delay in diagnosing bladder cancer (1,2). While this study was conducted in Brazil, other studies have demonstrated that Americans' overall cancer awareness is low (3). We have also recently demonstrated that basic knowledge and public education regarding bladder cancer is low (4).

So how are we to make an impact in the overall survival of patients with UUTT and bladder cancer? The authors appropriately stress that "widespread information could lower the stage at diagnosis." The risk factors for UUTT and bladder cancer need to be publicized; patients and primary care physicians need to be educated regarding the timely evaluation of hematuria; and ultimately, screening programs for those at high-risk need to be implemented.

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Extracorporeal Shockwave Lithotripsy versus Ureteroscopy for Distal Ureteric Calculi: Efficacy and Patient Satisfaction

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ABSTRACT

Objective: We compared the efficacy of extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) for the treatment of distal ureteral calculi with respect to patient satisfaction.

Materials and Methods: This is a prospective study where a total of 212 patients with solitary, radiopaque distal ureteral calculi were treated with ESWL (n = 92) using Dornier lithotripter S (MedTech Europe GmbH) or URS (n = 120). Patient and stone characteristics, treatment parameters, clinical outcomes, and patient satisfaction were assessed for each group.

Results: The 2 groups were comparable in regard to patient age, sex, stone size, and side of treatment. The stone-free status for ESWL and URS at 3 months was 81.5% and 97.5%, respectively ($p < 0.0001$). In addition, 88% of patients who underwent ESWL versus 20% who underwent URS were discharged home the day of procedure. Minor complications occurred in 3.3% and 8.3% of the ESWL and URS groups, respectively ($p = 0.127$). No ureteral perforation or stricture occurred in the URS group. Postoperative flank pain and dysuria were more severe in the URS than ESWL group, although the differences were not statistically significant ($p = 0.16$). Patient satisfaction was high for both groups, including 94% for URS and 80% for ESWL ($p = 0.002$).

Conclusions: URS is more effective than ESWL for the treatment of distal ureteral calculi. ESWL was more often performed on an outpatient basis, and showed a trend towards less flank pain and dysuria, fewer complications and quicker convalescence. Patient satisfaction was significantly higher for URS according to the questionnaire used in this study.

Key words: ureteral calculi; ureteroscopy; extracorporeal shockwave lithotripsy
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INTRODUCTION

Urinary lithiasis can cause a greater or lesser degree of obstruction of the lower ureter, depending on the size of the calculus, urothelial edema and the degree of impaction, requiring instrumental treatment, sometimes as an urgent procedure. In the past 25 years, the treatment of these calculi has evolved from ureterolithotomy to ureterorenoscopy URS (1), extracorporeal shockwave lithotripsy (ESWL) (2), and endoscopic lithotripsy (3,4).

Advances in the design of the ureteroscope and ongoing development in ESWL have greatly impacted the management of ureteric stones (5). The indications for ureteroscopic lithotripsy have increased with smaller semi-rigid ureteroscopes and reliable laser technology and the production of more robust flexible instruments has further expanded the indications for endoscopic intervention. Despite the definite success of endourological stone treatment, ongoing questions about optimum management remain debated among urologists.

ESWL and URS are currently accepted treatment modalities for distal ureteral calculi. Some authors (6,7) favor ESWL while others (8-10) prefer URS. For both treatment modalities stone-free rates of more than 90% have been reported (7,9,10).

The American Urological Association Ureteral Stones Clinical Guidelines Panel has found both to be acceptable treatment options for patients, based on the stone-free results, morbidity, and retreatment rates for each respective therapy. However, costs and patient satisfaction or preference were not addressed (11).

We aim to compare herein the efficacy and safety of ESWL and URS for distal ureteral calculi with respect to patient satisfaction.

MATERIALS AND METHODS

A total of 212 patients undergoing therapy for distal ureteral calculi between January 2001 and December 2004 were entered into the study. Patients presented with radiodense ureteral stones distal to the bony pelvis on excretory urogram or computed tomography (CT) which had not passed spontaneously within 3 weeks. Patients were included in the study only if the intervention, either ESWL or URS, was the primary modality and there was a minimum follow-up period of 3 months. Patients for whom either therapeutic modality was contraindicated because of pregnancy, urinary tract infection, coagulation disorders or previous ureteral reimplantation were excluded from the study.

After defining the indications of treatment, the patients were made aware of both the modalities of treatment and their probable complications. The need for anesthesia, stent, urethral manipulation, possible complications, need for repeated follow up especially after ESWL, and the cost factor involved, were explained to the patient. The patients were then asked to choose the mode of treatment.

ESWL was performed using the Dornier lithotripter S (MedTech Europe GmbH). All patients were positioned prone and the calculi were localized with fluoroscopic guidance. All patients were given sedatives and analgesics and the level of shockwave

energy was progressively stepped up till satisfactory stone fragmentation within the patient's comfort. URS was performed with rigid 8F Wolf ureteroscope following dilatation of ureteric orifice if needed. The stones were either extracted via basket or forceps, or disintegrated with the Pneumatic lithotripsy lithotripter. Placement of a ureteral stent at the conclusion of the procedure was left to the discretion of the treating surgeon. Upon completion of the procedure, fluoroscopic imaging was performed to determine whether the ureter was stone-free. All patients were administered prophylactic antibiotic.

Complete stone clearance was assessed at three months follow up. Patients were followed-up to assess the success rates and complications of the two procedures. The follow up schedule was similar in both groups of patients. Plain x-rays were obtained 1, 2, 4 and 6 weeks after discharge and thereafter if residual fragments persisted. Obstruction of the upper urinary tract was excluded from diagnosis with the help of ultrasonography. In case of recurrent ureteral colic or if calculi failed to pass within 6 weeks ureteroscopic stone removal was performed. Treatment failure was based on the need for further surgical intervention during follow-up or failure to become stone-free within 3 months (7). At initial follow-up, patients were given a questionnaire, which we use for all patients with urolithiasis in our center based on published data about the factors that influenced patient satisfaction (7,9) (Table-1). Those with total score of 8 or less were considered satisfied with the procedure. The efficiency quotient (EQ) was calculated using the formula: $\text{Stone free (\%)} \times 100 / (100 + \text{retreatment rate (\%)} + \text{rate of auxiliary procedures (\%)})$ (12).

Data were analyzed using Statistical Package for Social Sciences (SPSS, version 11.5). Pearson's chi-square, student t-test, Mann-Whitney U test was used where appropriate and $p < 0.05$ was considered statistically significant.

RESULTS

One hundred and twenty patients were treated with URS (male/female: 85/35), while 92 (male/

Table 1 – Postoperative questionnaire.

	0	1	2	3
Postoperative symptoms:				
Dysuria	No	Mild	Moderate	Severe
Hematuria	No	Microscopic	Macroscopic -no clots	With clots
Loin pain	No	Mild	Moderate	Severe
Time to normal activity	0-1 day	2-3 days	3-6 days	> 6 days
Global satisfaction	Yes	Not sure	No	
Willingness to repeat	Yes	Not sure	No	
Recommending the procedure	Yes	Not sure	No	

female: 70/22) patients were treated by ESWL. Patient's age varied between 11 and 75 years, with maximum number of patients between 35 to 45 years of age. There were no significant differences in the mean age, sex ratio and stone size in both groups (Table-2). For the extracorporeal modality, i.e. ESWL, the mean stone size was 10.4 ± 5.3 mm (range 4 to 27) (Table-2). In this group, 90% received intravenous sedation and 10% general anesthesia. Majority of the patients (88%) had treatments as an outpatient procedure but all patients needed frequent follow-up visits. Only 4 patients (4.3%) required pre-ESWL double pigtail stents for persistent ureteric colic not responding to conservative treatment. A total of 92 patients required 115 sessions of lithotripsy with average number of 3720 shock waves at 10-20 kV. Stone-free status at 1 month and 3 month were 67% (n = 62) and 81.5% (n = 75), respectively (Figure-1). There were no major complications, although three patients (3.3%) developed fever and infection. In total,

23 patients (25%) required more than one session of ESWL for disintegration, whereas 17 patients (18.5%) where ESWL failed were treated by URS for 16 cases and open ureterolithotomy for one patient with a hard 27 mm stone (Table-3). Of these, there were 4 cases of "steinstrasse" (4%) after ESWL and only 2 were treated conservatively; the other 2 required URS. EQ at 3 months was 57. Considerable differences with regard to patient satisfaction were noted with a mean score of 5.03 ± 3.08 . Of the patients 74 (80%) were satisfied and will recommend the procedure to the others while 18 (20%) who required re-treatment or URS would opt for URS for recurrence (Table-3).

For the intracorporeal modality, i.e. URS with pneumatic lithotripsy, the mean stone size was 9.2 ± 5.4 mm (range, 4 to 27) (Table-2). In this group, 60% of patients had general anesthesia, 25% local anesthesia and 15% intravenous sedation. The majority of the patients had treatments as an inpatient procedure (80%) mainly for 'social' reasons, like difficulty

Table 2 – Baseline comparability of the 2 treatment groups.

	ESWL	Ureteroscopy	p Value (t-test)
N patients	92	120	0.104*
Mean age \pm SD (year)	42.3 ± 12.0	45.3 ± 14.0	0.394†
Male to female ratio	1: 0.3	1: 0.4	0.121*
Mean stone size \pm SD (mm)	10.4 ± 5.3	9.2 ± 5.4	0.979†
N stones Rt./Lt. side	42/50	55/65	

* t-test, † chi-square test.

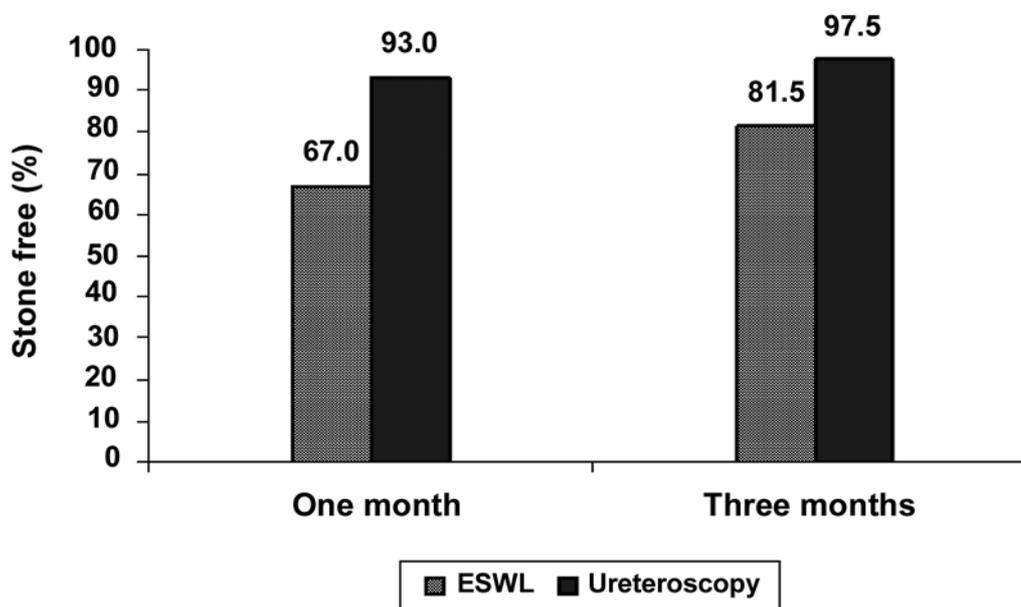


Figure 1 – Stone free rate at 1 month and 3 months.

in transport. Some of these were admitted for pain control, infection and stent-related symptoms but all patients needed less frequent visits for follow-up than ESWL. After URS, ureteric catheter or double J stent was kept in 41 patients (34.2%) for 24 hours to 3 weeks. Of these, 12 patients (10%) required postoperative double-J ureteric stenting due to high stone load. In 28 cases (23%), the calculi could be extracted

without fragmentation (forceps retrieval in 17 and basket retrieval in 11) and all other stones were fragmented using the Pneumatic lithotripsy lithotripter. Repeat URS was however required in 8 patients (6.7%) after 4 weeks (Table-3). EQ at 3 months was 89. In these patients the initial attempt of URS failed due to failure to adequately dilate the ureteric orifice in six and submucosal dissection with false passage

Table 3 – Results of ESWL versus Ureteroscopy.

	ESWL	Ureteroscopy	p Value (t-test)
N of auxiliary procedures	17 (18.5%)	3 (2.5%)	< 0.0001*
Complications	URS and open 3 (3.3%)	ESWL and open 10 (8.3%)	0.127*
Mean follow-up ± SD (weeks)	5.8 ± 3.0	4.2 ± 3.4	< 0.0001†
N of re-treatment	23 (25.0%)	8 (6.7%)	< 0.0001*
Patient satisfaction	74 (80.4%)	113 (94.2%)	0.002*
Postoperative analgesia	68 (73.9%)	104 (86.7%)	0.019*
Mean period of analgesia ± SD (days)	1.9 ± 1.5	2.4 ± 1.5	0.029†
Efficiency quotient at 3 months	57	89	

* Chi-square test, † Mann-Whitney U test.

in two patients. Open surgery was required for one of these patients who had a hard 25 mm stone. The proximal migration of calculus occurred in 2 patients (1.7%) who were treated by ESWL. Mean hospital stay in URS was two days. With respect to complications, there were 6 cases (5%) of infection in addition to 2 cases of proximal stone migration and 2 cases of submucosal dissection. No long-term complications, such as ureteric stricture, were documented during the follow-up period. Oral pain medication was used in 86% of the URS compared with 74% of ESWL cases ($p = 0.019$), for a significantly longer duration (2.4 ± 1.5 versus 1.9 ± 1.5 days, respectively, $p = 0.029$). Follow-up was significantly shorter for the URS group (4.2 ± 3.4 versus 5.8 ± 3.0 weeks, $p = 0.0001$) (Table-3). Stone-free status at 1 month and 3 months were 93% and 97.5%, respectively (Figure-1). The mean satisfaction score was 4.03 ± 2.08 which is significantly different from the ESWL group ($p = 0.043$). Overall, 113 patients (94%) were completely satisfied with the therapeutic modality chosen and will recommend it to the others except for the 7 patients who required re-treatment or open surgery and preferred to undergo ESWL for recurrence (Table-3).

COMMENTS

Ureteric stones have a high probability of spontaneous clearance. Spontaneous passage should be favored if possible (11,13). According to a meta-analysis by the AUA Guidelines Panel, newly diagnosed stones with a diameter < 5 mm will pass in up to 98%, depending on the degree of obstruction, urothelial edema and degree of impaction (11). With close controls and in absence of risk factors like impaired renal function, pain, urinary tract infection or fever, these stones can be followed safely until spontaneously cleared. However, most authors recommend not exceeding 4-6 weeks, especially for obstructive ureteric calculi (14,15). These data show that the success rate is strongly influenced by the timing of therapeutic intervention (9). The sooner therapy is initiated, the more stones that might have passed spontaneously will be treated and, thus, false results in favor of the chosen procedure will be

obtained. In particular small stones have a high spontaneous passage rate and so therapeutic intervention should be delayed to allow clearance (9). For this reason treatment was delayed in our study until 3 weeks after the diagnosis of a prevesical stone unless earlier therapeutic intervention was mandatory because of recurrent colic.

Peschel et al. (9) have reported on the differences that they have encountered in dealing with distal ureteral calculi with both ESWL and URS (rigid or semi-rigid). URS was significantly better in terms of shorter operative time, fluoroscopy time and time to achieve a stone free status. The authors recommend URS as first-line treatment for smaller stones (< 5 mm) that do not pass spontaneously.

In our series patient satisfaction was uniformly high in both groups but only significantly higher for URS (94 %) compared to shock wave lithotripsy (80%) ($p = 0.002$). Also, patient willingness to undergo a repeated procedure of the same type favored URS. No true validated instrument exists for comparing patient symptoms and satisfaction with these different treatment options (16).

The efficacy of the treatment cannot be only judged by the stone free rate but various other parameters like postoperative symptoms, patient willingness to undergo a repeated procedure or to recommend it and the time of return to normal activity. The satisfaction criteria in this study were more extensive. In our series from the patient viewpoint achieving a stone-free state as soon as possible is the ultimate goal once the therapeutic approach has been chosen by most of the patients.

Patient satisfaction generally reflected treatment success. When assessing the efficacy of treatment an important consideration is the time it takes to achieve a stone free status. Peschel et al. (9) also concluded that in this respect there are considerable differences between ESWL and URS. Results of their patient assessment clearly demonstrated how important it is to achieve a stone free state early and even the patients who were free of symptoms said that the awareness of residual stone fragments and fear of colic were an ever present source of discomfort and restricted their ability to perform daily activities. Therefore, most patients in

their study were satisfied with URS but would not be satisfied with ESWL. Pearle et al. (7) found no significant difference in postoperative symptoms between the 2 treatment groups despite the presence of a ureteral stent in virtually all patients who underwent URS but only 16% of the ESWL group. Their sample size may preclude statistical significance but there was a definite trend towards fewer symptoms in regard to bladder irritability with shock wave lithotripsy. The ESWL group used less pain medication for a shorter period compared with the URS group, and patient satisfaction slightly favored ESWL (7). They recommended ESWL with a HM3 lithotripter as first-line treatment for distal stones. In our series, oral pain medication was used by 74% of the ESWL group compared to 86% of the URS cases, ($p = 0.019$), and the duration of analgesic use was significantly longer in the URS group ($p = 0.029$). Despite this our patients favored URS because of the longer time to obtain a stone free status with the ESWL in addition to the other parameters in the questionnaire. In this respect our results are in agreement with those of Peschel et al. (9).

From a retrospective review of planned same-day discharge after ureteroscopy in 114 patients, Wills and Burns (17) concluded that ureteroscopy should be considered an outpatient procedure. They reported a 24% immediate admission rate, with about half the admissions for "social" reasons. The inclusion of social components within our routine assessment minimizes admission required for social reasons. Our patients have difficulty in transports as they live far away from the hospital.

Given the high success rates for both treatment modalities in our study, treatment success must also consider secondary outcome parameters, such as complications rates, patient satisfaction, procedural efficacy and cost. Complication rates are low for the treatment modalities. In neither the series of Pearle et al. (7) or Peschel et al. (9) did ureteral perforation or stricture occur in either treatment group. However, ureteral injury is an established, albeit rare, complication of URS that has never been reported to occur with in situ shock wave lithotripsy. Furthermore, complications associated with ESWL are generally mild and related to fragment passage. In our series,

although not reaching statistical significance, an almost 3-fold increase in minor complications occurred with URS compared to ESWL. Consequently, ESWL is a marginally safer modality associated with few if any long-term sequelae.

However, the invasiveness of ureteroscopy cannot be neglected. Before the emergence of modern techniques for stone fragmentation and newer, better-designed ureteroscopes, complications like ureteric perforation and avulsion were not uncommon. A comprehensive review of acute endoscopic injuries reported in the literature from 1984 to 1992 identified 314 ureteric perforations that occurred in 5117 procedures (6.1%) and complete ureteric avulsion in another 17 procedures, though infrequent, were documented (0.3%) (18). Harmon et al. (19) observed a decrease in overall complications from 20% to 12% during a 10-year period which were attributed to smaller ureteroscopes and increased surgeon's experience. Schuster et al. (20) suggested a significant reduction in ureteric perforation with a less operative time and postoperative complications with the surgeon's experience. Proximal migration of stones occurred in 2 patients (1.7%), which is less than what had been reported. (21,22). With the emergence of flexible ureteroscopes, migrated stones could be retrieved with basket. However, these state-of-the-art ureteroscopes are fragile and experience in our center is still limited. We still use semi-rigid ureteroscopes for all ureteric calculi.

In our study, only 12 patients (10%) of the URS group had a double-J ureteric stent inserted for high stone load while 29 patients (24.2%) had ureteric catheters for 24 hours. This significantly reduces the occurrence of colic, hematuria and other complications of obstruction. In the majority of patients undergoing uncomplicated URS for removal of distal ureteral calculi postoperative discomfort is modest, lasts less than 2 days and is easily controlled with oral analgesics. Stricture formation has not been identified. Hence, we do not believe that routine placement of a ureteral stent following uncomplicated URS for a distal ureteral calculus is necessary. Routine placement of ureteral stent after ureteroscopic stone has been considered the standard of care in most centers but Denstedt et al. (23) performed a prospective trial of non-stented versus

stented ureteroscopic lithotripsy, and concluded that patients without a stent have significantly fewer symptoms in the early post-operative period, while there were no differences in terms of complications and stone free status. In addition it is also important to notice that with ESWL, more follow-up visits to the clinic were required until a stone-free state was achieved and at each visit, the patient was exposed to radiation from plain radiography.

Some investigators concluded that prophylactic antibiotic during ESWL are unnecessary in patients whose urine before treatment was sterile (24), other studies showed that antibiotic prophylaxis with several agents can reduce the rate of bacteriuria significantly (25). Currently, many urologists routinely prescribe antibiotic prophylaxis to reduce the potential risk.

On the other hand, an important disadvantage of URS is that the procedure has to be performed under general or spinal anesthesia as compared to ESWL, which uses intravenous analgesia. This exposes the patient to the risks of anesthesia and makes it unfavorable to patient with significant medical problems but there are some reports on local anesthesia combined with intravenous sedation for URS (26,27). From our series local anesthesia with intravenous sedation were sufficiently effective and safe in our patients with good tolerance. The need for anesthesia during ESWL depends largely on the energy source. While spark gap lithotripters (HM-3, MFL 5000) are highly effective, they are also more painful for the patient, whereas piezoelectric shock wave lithotripsy is associated to the least pain yet low efficacy. We could not find difficulty in stone localization under sedation with the Dornier Lithotripter S. We suggest that the choice of treatment modality for ureteric stones will depend on the patient since the expertise for both modalities are equally available. Patient's factors will include acceptance of invasive procedure, physical health and preference for earlier stone-free status.

The American Urological Association (AUA) Guidelines Panel (11) reported its recommendations for the treatment of ureteric stones. Although this report was clear in its recommendations of in situ shock wave lithotripsy

for the treatment of small ureteral calculi, it was less clear for the large (> 1 cm) upper ureteric stones. Although ESWL, URS, percutaneous stone extraction and open surgery were evaluated as different options; laparoscopic ureterolithotomy was not mentioned. Indeed, the previously mentioned treatment options have rendered open procedures a rarity in many hospitals (28). Open surgery was required for two of our patients with hard large stones. Sharma et al. (29) reported that open mini-access ureterolithotomy to be a safe and reliable minimally invasive procedure; its role is mainly confined to salvage for failed first-line stone treatments but in selected cases, where a poor outcome can be predicted from other methods, it is an excellent first-line treatment. Laparoscopy has the advantage of high probability of removing the entire stone in one procedure, exactly like open surgery.

Success rates for shock wave lithotripsy may differ according to the lithotripter used. Average stone-free rate for cumulative shock wave lithotripsy series in the literature using an HM3 lithotripter is slightly but consistently higher than that achieved with many second and third generation lithotripters and may influence the choice of treatment (30). It is important to stress that the results with shock wave lithotripsy are truly machine specific and cannot be translated to use with other lithotripters (31).

The Dornier Lithotripter S that we use, proved in different series to be very effective in the treatment of renal and ureteral calculi (32). Though this is not randomized prospective study, matching the two groups in terms of age, sex and stone size and studying consecutive patients managed by the same group of urologists minimize patient selection bias.

In summary, ESWL offers minimal-invasiveness but a higher risk of treatment failure compared to URS which reaches immediate high stone free rates. ESWL is a marginally safer modality associated with few if any long-term sequelae. Treatment decisions have to be drawn individually taking into account patients preference, personal experience and local equipment. We believe that ureteroscopy is preferable to ESWL for treatment of distal ureteral calculi since it is significantly more efficient with higher patient satisfaction.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Ghalayini and colleagues have prospectively studied the efficacy and patients satisfaction in a comparative non-randomized study comparing ureteroscopy and shock wave lithotripsy for distal ureteric stone. An informed consent was taken and patients opted for one or the other treatment arm.

The authors have done this study quite amicably and should be congratulated for the honest description of the results. However, there are several factors that should be emphasized before incorporating their findings into every day clinical practice.

Efficacy of the treatment for distal ureteric stone is judged not only by stone free rate but other factors like need for re-treatment, ancillary procedure requirement and admission, all but the last are analyzed by efficient quotient (1-3). In this work 80% patient falling ureteroscopy required hospitalization, this is contrary to contemporary experience as admission following ureteroscopy for distal ureteric

stone is only required in a small minority. Most often it is for social reason, lack of follow-up, health care facility (home care, trained general practitioner etc) and less commonly for complications.

The other major difference between ureteroscopy and shock wave lithotripsy is the quantum of complications. The incidence of major complications like ureteric avulsion and ureteric perforations are fortunately rare but still a potential possibility. In the present work, the authors have found a very low incidence of complications in the 2 groups with no major complication. Need for anesthesia is another major difference between the 2 procedures. Although in women with distal ureteric calculi requiring treatment, ureteroscopy could be done under intravenous sedation, in men the better tolerance of SWL must be weighed against the higher success rate of ureteroscopy. If both treatment modalities are available, patients with small distal ureteric calculi,

in whom ureteroscopy is likely to be successful, should be informed of and offered their choice of either treatment modality. Overall, the study adds nicely to rapidly growing body of evidence that ureteroscopy is a better option of treatment for stones moderately large to larger stones (3).

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EDITORIAL COMMENT

The aim of surgical management of ureteral calculi is to obtain complete stone free state with minimal morbidity to the patient. Ureteral calculi are often associated with obstruction and treatment should be done to prevent irreversible damage to the kidney. Mainly 3 factors are important for the selection of treatment modality. First stone related factors i.e. stone localization, size, composition, duration, degree of obstruction, second clinical factors as patient tolerance to intervention, symptomatic events, patient expectations, infections, solitary kidney, abnormal anatomy and the third, technical factors i.e. available equipment and cost.

Considerable progress has been made in the medical and surgical management of urolithiasis over the past 25 years. Three minimally invasive techniques are currently available, which significantly reduced the morbidity of stone removal: percutaneous nephrolithotomy (PNL), rigid and flexible ureterorenoscopy (URS) and shock wave lithotripsy (SWL). For many clinicians, ureteroscopy with extraction or intracorporeal lithotripsy is the preferred

treatment of distal ureteral calculi. However, shock wave lithotripsy with or without stent implantation is the treatment of choice in some centers. Studies suggest that either SWL or URS are useful options for the management of distal ureteral calculi. Ureteroscopic access is frequently useful for the management of ureteral calculi when shock wave lithotripsy is failed and for complex calculi because shock wave lithotripsy is not the ideal modality for the management of this kind of calculi. Several investigators do not advocate the use of shock wave lithotripsy for the treatment of distal and prevesicular stones due to difficult positioning of the patients for these procedures in which prone or modified sitting position is preferred in these situations. The advances in the fiber optic lens systems resulted in the manufacturing of smaller ureteroscopic instruments, which enabled widespread use of routine diagnostic and therapeutic procedures within the ureter and kidney. Open surgery is rarely preferred today but it remains as an option for a salvage procedure. Alternatively laparoscopic surgery is a minimally

invasive option that can be used in circumstances where open surgery may have been indicated.

As this study showed URS and ESWL modalities share an overall high success rate with low morbidity and both modalities has also proven to be effective and safe therefore the selection of the optimal treatment for distal ureteral calculi remains one of the most controversial issues currently in endourology.

Although ureteroscopic treatment is more invasive than ESWL the patient may achieve a stone free status with a single procedure. ESWL is less invasive but a drawback from the patients' perspective may be the long follow-up until a stone free state or the risk of a requirement for additional invasive procedures and retreatment need associated with ESWL. Conversely patient may favor ESWL because of fear of the anesthesia requirement associated with ureteroscopy and the possibility of a temporary ureteral stent implementation. ESWL can be done as an outpatient procedure with sedation.

ESWL is equivalent to URS for smaller stones (less than 1 cm) but becomes significantly less efficient with larger stones. Generally ESWL was recommended for small and solitary stones, and URS for large or multiple stones. Not expectedly, smaller stones (less than 5 mm) that had not passed spontaneously by 3 weeks can be more efficiently treated with URS, because they are the most difficult to localize and focus with ESWL.

A review of the literature revealed that the mean stone free rate for ESWL are 50-95% and for ureteroscopy 96-100%, retreatment rates are 27-50% for ESWL and 0.8-19% for ureteroscopy.

Recent studies suggest a tendency from noninvasive ESWL to ureteroscopy. As depicted in the current study patient satisfaction is also better in URS.

Choice of treatment modality depends on the current data regarding effectivity, complications and cost-effectiveness, physicians' expertise and available equipment. The patients preferences as anesthesia acceptance or deny and immediate cure expectations are also the factors that effecting the choice. The patient should be informed for the existing active treatment modalities and their relative benefits and risks.

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EDITORIAL COMMENT

The optimal treatment for distal ureteral stones remains an important question in urology. While there have been multiple studies addressing

this issue, there have been only 2 prospective randomized trials to date, each with a contradictory answer. In a multi-institutional trial Pearle et al. (1)

concluded that shock wave lithotripsy is preferable while Peschel et al. (2) instead determined that ureteroscopy should be first line treatment. Of note, these conclusions were not based on stone free rates alone, but instead included results from patient questionnaires addressing postoperative pain and satisfaction. Due to its non-randomized study design and inherent risk of selection bias, this work by Ghalayini and colleagues does not provide the definitive answer for the treatment of distal ureteral stones. However, it does provide an interesting insight into what patients find important regarding their procedure. Despite taking significantly less oral pain medication for a shorter period of time and having fewer complications, patients in the shock wave lithotripsy group had a lower level of satisfaction than patients undergoing ureteroscopy. It is important to note that the questionnaire used to obtain these results has not been validated, but it is clear that the global assessment of patient satisfaction was composed of more than just postoperative discomfort. The authors suggest that the decreased satisfaction in the shock wave

lithotripsy group was due to the more prolonged time for stone passage relative to ureteroscopy. While no analysis was performed directly addressing this conclusion, shorter time to stone passage following ureteroscopy is a possible explanation as to why patients favored a procedure that was clearly more painful. Definitive proof supporting this conclusion will require further study, but when counseling patients on shock wave lithotripsy versus ureteroscopy for treatment of distal ureteral stones, the patient's feelings regarding stone passage time may help suggest one procedure over the other.

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Microvascular Invasion Is an Independent Prognostic Factor in Patients with Prostate Cancer Treated with Radical Prostatectomy

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ABSTRACT

Objective: Current published data regarding the prognostic value of microvascular invasion (MVI) in patients with prostate cancer (PCa) have yielded mixed results. Furthermore, most important series had surgical procedures performed by multiple surgeons and surgical specimens analyzed by multiple pathologists. We determined the relation of MVI with other pathologic features and whether this finding can be used as an independent prognostic factor in patients with PCa.

Materials and Methods: We selected 428 patients with clinically localized PCa treated with radical prostatectomy (RP). MVI was correlated to other pathologic features. The Kaplan-Meier method was used to evaluate survival curves and statistical significance was determined by the log-rank test. Multivariate analysis was performed through a Cox proportional hazards regression model.

Results: Eleven percent out of the 428 patients presented MVI. Except for the lack of association with biopsy Gleason score, MVI was related to all clinical and pathologic features of RP specimens. Mean follow up after surgery was 53.9 ± 20.1 months. Patients with MVI presented a recurrence rate of 44.6% compared to only 20.2% for patients without MVI (Log-rank test - $p < 0.001$). After Cox regression analysis, MVI was an independent prognostic feature related to biochemical recurrence.

Conclusions: MVI is associated to advanced pathologic features of PCa and is an important prognostic factor regarding disease recurrence in patients treated with RP. These findings support the recommendations to the routine evaluation of this variable in pathologic reports of RP specimens.

Key words: prostate; prostatic neoplasms; prostatectomy; survival analysis; disease progression

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INTRODUCTION

Despite surgical treatment, almost 30% of the patients presenting clinically localized prostate cancer (PCa) will develop elevation of serum prostate specific antigen (PSA) in a 10 years follow up period (1). For this reason, one of the most important

challenges for urologists is the identification of patients with a high risk of disease progression that may benefit from adjuvant therapies.

To date, histological characteristics of PCa in radical prostatectomy (RP) specimens as

pathological stage, final Gleason score, seminal vesicle involvement, surgical margin status, level of extraprostatic extension and tumor volume are frequently used to predict progression after surgery (2). According to recommendations of the College of American Pathologists Cancer Committee since 1994, microvascular invasion (MVI) is reported in RP specimens (3), even though mixed results regarding its incidence and prognostic significance are reported in literature.

Incidence rates of MVI in RP specimens range from 5 to 53% (4-10). While many studies have found that MVI is a significant predictor of disease progression only in univariate analysis (4,10), others have reported its independent significance in multivariate analysis (8,9,11). Furthermore, the most important series had surgical procedures performed by multiple surgeons and surgical specimens analyzed by multiple pathologists, leading to possible interpretation biases.

In the present study, the authors sought to determine the prognostic significance of MVI in predicting biochemical recurrence after surgery in a group of patients with PCa treated with RP performed by a single surgeon and with surgical specimens analyzed by a single pathologist, enhancing the uniformity of MVI assessment and other pathologic variables.

MATERIALS AND METHODS

From August 1993 to November 2000, we selected 428 patients with PCa treated with RRP. Patients with insufficient clinical data or that had undergone neoadjuvant or adjuvant treatments were excluded from the study. All cases had clinically organ confined disease suspected by high serum PSA or palpable nodule at digital rectal examination and were diagnosed by transrectal ultrasound-guided needle biopsy. Surgical procedures were performed only by one surgeon (MS) and the pathology samples analyzed by only one pathologist (KRL). Staging evaluation consisted of history, physical examination, serum PSA, MVI, computed tomography, bone scan and TUNB. The clinical staging was determined using the

1992 AJCC staging system (12). Tumor grading was assessed according to the Gleason system (13).

The specimens of RP were submitted to histological study in accordance with the previously described recommendations (14). Thin transversal sections were performed in the surgical margins related to the bladder neck and the prostate apex. Seminal vesicles were sectioned in the base and longitudinal sections were submitted to histological examination. The entire gland was included for study after having their margins painted with India ink. Sequential transversal sections were performed every 3 mm, designed from the proximal region towards the distal one. Approximately 10 or 12 sections from each lobe were included for histological study. The lymph nodes from the fat related to the resection of the iliac chain were dissected and included for study. The specimens of RP underwent the usual processing with inclusion in paraffin. MVI was defined as the presence of tumor cells within an endothelium lined spaces.

Mean patient age at diagnosis was 62.8 years (range 40 to 83), and mean PSA was 10.0 ng/mL. Three hundred and thirty five (78.2%) of the 428 patients presented Gleason score of six or less, and about 50% had non-palpable disease (T1c). The mean percent positive biopsy cores (PPBC) was 41% (range 5 to 100%). After pathological examination, 72.1% of the patients showed organ confined disease (T2) and no patient showed lymph node involvement.

Patients were examined at month 2 postoperatively, and then every 6 months for 5 years and annually thereafter. At every follow up, digital rectal examination was performed and serum PSA measured. Disease recurrence was defined as a serum PSA of 0.4 ng/mL or greater.

To analyze the clinical and pathological variables according to the MVI, we used the Student's t-test, Fisher exact test and qui-squared test. PSA and PPBC were analyzed as continuous and categorical variables. To analyze the value of the pre-operative clinical and pathological parameters in predicting the presence of MVI at surgical specimen, we used a logistic regression model with adjusted proportional risks. Kaplan Meier method was used to estimate the survival curves and to compare the curves we used the

log-rank test. A survival analysis, considering biochemical recurrence as the main end point was done through a Cox regression model. Statistical significance was set as $p \leq 0.05$. Statistical analysis was performed using the SPSS 12.0 for Windows software.

RESULTS

MVI was found in 47 (11%) of the 428 patients (CI 95% [8.2% to 14.3%]). Table-1 lists clinical and pathological characteristics according to the presence of MVI. Serum PSA, analyzed as a continuous or categorical variable showed statistical association with the presence of MVI. While only 5% of patients with PSA under 4 ng/mL had MVI, this finding was observed in almost 30% of patients with PSA greater than 20 ng/mL. Mean PPBC among patients with MVI was

53% vs. 39% in patients without MVI. Likewise, about 21% of patients with more than 50% positive biopsy cores had MVI and only 8% of patients with 50% or less positive cores had this finding ($p = 0.001$). Regarding clinical stage, MVI rates were significantly higher among patients with T2 when compared to patients with non-palpable disease.

Table-2 lists postoperative pathological characteristics according to the presence of MVI. Regarding pathological stage, MVI was found in 20.2% of patients with T3 vs. 10.9% of the patients with T2B + T2C disease. Patients with T2A disease presented the lowest MVI rates. Patients with final Gleason score 8 or 9 presented 31.8% of MVI compared to only 5.8% among patients with final Gleason score between 4 and 7.

In logistic regression analysis to determine the risk of MVI at surgical specimen, we found that

Table 1 – Preoperative variables according to the presence of microvascular invasion (MVI).

	Microvascular Invasion		p Value
	Yes (N = 47)	N (381)	
Age (years)	63.8 ± 7.2	62.7 ± 7.5	0.372*
PSA (mean)	10.6 [8.6 ; 13.1]	8 [7.5 ; 8.5]	0.004**
PSA			0.006***
≤ 4.0	2 (5.0%)	38 (95.0%)	
4.1 to 10.0	21 (8.3%)	232 (91.7%)	
10.1 to 20.0	15 (14.7%)	87 (85.3%)	
> 20.0	9 (27.3%)	24 (72.7%)	
Gleason score			0.169***
≤ 6	33 (10.8%)	302 (90.2%)	
7	8 (12.5%)	56 (87.5%)	
≥ 8	6 (20.7%)	23 (79.7%)	
PPBC	52.9% ± 28.0%	39.3% ± 23.0%	< 0.001*
PPBC			0.006***
≤ 25.0%	11 (7.8%)	130 (92.2%)	
25.1 to 50.0%	16 (8.4%)	174 (91.6%)	
50.1 to 75.0%	10 (16.7%)	50 (83.3%)	
75.1 to 100.0%	10 (27.0%)	27 (73.0%)	
Clinical stage			0.003****
T1	14 (6.5%)	201 (93.5%)	
T2	33 (15.5%)	180 (84.5%)	

* Student's t test; ** Log-transformed student's t test; *** Fisher exact test generalized; **** Fisher exact test; PPBC = percent of positive biopsy cores.

Table 2 – Postoperative variables according to the presence of microvascular invasion.

	Yes (N = 47)	N (381)	p Value
Capsular involvement			< 0.001*
Yes	43 (18.5%)	189 (81.5%)	
No	4 (2.0%)	192 (98.0%)	
Seminal vesicle involvement			0.030**
Yes	6 (26.1%)	17 (73.9%)	
No	41 (10.1%)	364 (89.9%)	
Pathological stage			< 0.001***
T2A	3 (2.4%)	123 (97.6%)	
T2B	13 (13.7%)	82 (86.3%)	
T2C	7 (8.0%)	81 (92.0%)	
T3A	18 (19.8%)	73 (80.2%)	
T3B	1 (20.0%)	4 (80.0%)	
T3C	5 (21.8%)	18 (78.2%)	
Gleason score			< 0.001*
4 to 6	12 (4.7%)	245 (95.3%)	
7	8 (9.3%)	78 (90.7%)	
8 to 9	27 (31.8%)	58 (68.2%)	
Margin status			> 0.999*
Positive	38 (11.0%)	307 (89.0%)	
Negative	9 (10.8%)	74 (89.2%)	

* Qui-square; ** Fisher exact test; *** Fisher exact test generalized.

while serum PSA, PPBC and clinical stage showed statistical significance in univariate analysis, only serum PSA (OR- 6.59; CI 95% [1.27 to 34.33]; p = 0.025) and clinical stage (OR- 2.31; CI 95% [1.17 to 4.57]; p = 0.016) remained significant variables on multivariate analysis. Biopsy Gleason score showed no relation with MVI risk.

Mean follow-up after surgery was 53.9 ± 20.1 months. Of the 428 patients, 98 (23%) presented disease recurrence, six (1.4%) developed clinical metastasis, and no one died of PCa. Using the log rank test, we found that patients with MVI had a 44.6% probability of disease recurrence vs. 20.2% among patients without MVI (p < 0.001) (Figure-1).

On univariate Cox proportional hazards regression analysis, all clinical and pathological characteristics but patient age and biopsy Gleason score were significantly associated with an increased risk of biochemical progression after surgery (Table-3). However, on multivariate analysis, only serum PSA, clinical stage, capsular involvement, surgical

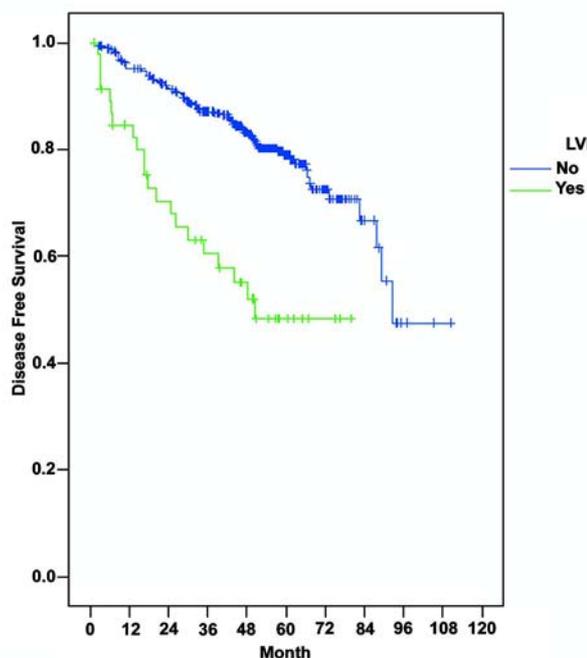


Figure 1 – Biochemical recurrence according to microvascular invasion (log-rank: p < 0.001).

Table 3 – Cox regression for the risk of biochemical recurrence (univariate analysis).

	Hazard Ratio	95% CI	p Value
Age (years)	1.03	[1.00 ; 1.06]	0.055
PSA			< 0.001
(4.1 to 10.0) /(0 to 4.0)	8.57	[1.18 ; 62.25]	0.034
(10.1 to 20.0)/(0 to 4.0)	17.32	[2.37 ; 126.78]	0.005
(> 20.0) /(0 to 4.0)	19.10	[2.50 ; 146.13]	0.005
PPBC			< 0.001
(25.1 to 50%)/(< 25.%)	1.51	[0.89 ; 2.58]	0.129
(50.1 to 75%)/(< 25.%)	2.10	[1.10 ; 4.00]	0.025
(75.1 to 100%)/(< 25.%)	4.00	[2.12 ; 7.54]	< 0.001
Biopsy Gleason score			0.073
7/(2 to 6)	1.74	[1.04 ; 2.89]	0.034
(8 to 10)/(2 to 6)	1.55	[0.74 ; 3.22]	0.245
Clinical stage			
(T2/T1)	2.34	[1.53 ; 3.57]	< 0.001
MVI			
(Yes/No)	3.17	[1.95 ; 5.16]	< 0.001
Seminal vesicle involvement			
Yes/No)	2.99	[1.69 ; 5.30]	< 0.001
Capsular involvement			
(Yes/No)	3.17	[1.99 ; 5.06]	< 0.001
Pathological stage			< 0.001
(T2B+T2C)/(T2A)	2.50	[1.32 ; 4.76]	0.005
(T3A+T3B+T3C)/(T2A)	4.76	[2.51 ; 9.02]	< 0.001
Final Gleason score			0.007
7/(2 to 6)	1.44	[0.85 ; 2.42]	0.175
(8 to 10)/(2 to 6)	2.09	[1.32 ; 3.33]	0.002
Margin status	2.02	[1.31 ; 3.10]	0.001
(Positive/Negative)			

PPBC = percent of positive biopsy cores; MVI = microvascular invasion.

margin status and the presence of MVI were significantly associated with biochemical recurrence (Table-4).

COMMENTS

In the present study, we found MVI in 11% of the 428 patients. This finding is similar to other reported series (9). However, discrepant rates have also been reported, and this fact is probably caused by different criteria in defining MVI, interobserver

interpretation, specimen handling, and by patient selection. McNeal & Yemoto (6), analyzing a similar group of patients with clinically localized disease found a 14% incidence rate, Herman (8), studying only patients with T3 tumors found a 35% rate, and Salomao et al. (5), found an overall incidence of 53%. The lower incidence observed in our study could be explained by a selection bias since more than 70% of patients had organ confined disease and no one showed lymph node involvement. However, as surgical specimens were analyzed by a single pathologist, the uniformity of MVI assessment and

Table 4 – Cox regression for the risk of biochemical recurrence (multivariate analysis).

	Hazard Ratio	95% CI	p Value
PSA			0.010
(4.1 to 10.0)/(0 to 4.0)	8.77	[1.18 ; 65.24]	0.034
(10.1 to 20.0)/(0 to 4.0)	13.99	[1.86 ; 105.00]	0.010
(> 20.0)/(0 to 4.0)	15.89	[2.03 ; 124.54]	0.008
PPBC			0.085
(25.1 to 50%)/(< 25%)	1.15	[0.66 ; 1.99]	0.629
(50.1 to 75%)/(< 25%)	1.16	[0.59 ; 2.29]	0.664
(75.1 to 100%)/(< 25%)	2.23	[1.15 ; 4.32]	0.017
Clinical stage			
(T2/T1)	1.87	[1.19 ; 2.95]	0.007
MVI (Yes/No)	1.78	[1.06 ; 2.97]	0.029
Capsular involvement (Yes/No)	2.15	[1.30 ; 3.57]	0.003
Margin status (Positive/Negative)	1.67	[1.06 ; 2.62]	0.028

PPBC = percent of positive biopsy cores; MVI = microvascular invasion.

other pathologic variables support the reliability of our results.

We also confirmed the correlation between MVI and other clinical and pathological characteristics of PCa. Regarding preoperative variables, MVI was associated with an increasing PSA, increasing PPBC and with an advanced clinical stage. Capsular and seminal vesicle involvement, increasing Gleason score and an advanced pathological stage were also associated with MVI postoperatively. Logistic regression analysis showed that patients with preoperative PSA greater than 20 ng/mL or palpable (T2) disease had 6.5 and 2.3 times the risk of presenting MVI on surgical specimen respectively.

Regarding biochemical recurrence after RP, our study also supports MVI as an independent prognostic variable. This finding was reproduced by other authors. McNeal and Yemoto (6), analyzing 357 radical prostatectomy specimens, found that the only independent predictors of biochemical recurrence were MVI, carcinoma grade, and cancer volume. de la Taille (9), analyzing 241 patients, found that biochemical recurrence-free survival was 92.5% for the patients without MVI as compared to 30.1% for patients with MVI on prostate specimen examination.

MVI, preoperative PSA and pathological stage were independent prognostic variables of biochemical recurrence. Likewise, Ito et al. (11), found that MVI along with Gleason grade and capsular penetration, were disease recurrence independent prognostic factors. Herman et al. (8), found a significant correlation between MVI and increasing tumor volume, increasing Gleason grade, level of extra-prostatic extension and the presence of seminal vesicle involvement. At 5 years, 45% and 21% of patients with and without MVI respectively presented disease progression. In multivariate analysis, MVI showed independent significance in predicting disease progression. More recently, Ferrari et al. (15), found a significant correlation with high Gleason grade, extracapsular extension, seminal vesicle invasion, increasing cancer volumes, positive margins, and elevated preoperative PSA levels. MVI was a strong and independent predictor for disease recurrence, however, in contrast to our study, the surgical procedures in this series were performed by several surgeons and it is possible that different surgical techniques have affected outcomes in the study group.

Conversely, to these reports, Bahnson et al. (4), described that despite the association of MVI with a fourfold greater incidence of progression and or

death, in multivariate analysis, its prognostic significance was dependent upon tumor grade. More recently, Shariat et al. (10), confirmed the association of MVI with features of biologically aggressive PCa and found a strong association between MVI and metastasis to regional lymph nodes. These findings suggest that MVI precedes or occurs coincidentally with lymph node metastasis, however MVI was not an independent prognostic factor for biochemical recurrence on multivariate analysis. These results could be attributed to the short follow up period (median 21 months). Again, multiple surgeons and pathologists were involved in this report, contributing to possible interpretation biases.

Some limitations in this study should be considered. Since no patient presented lymph node involvement, this variable could not be related to MVI or used in multivariate analysis. Furthermore, despite our mean 53.9 months follow-up being longer than most previous studies analyzing MVI, the number of patients who developed clinical metastasis was limited (only six), and no one died of PCa. This fact limits the power of our study to analyze associations between these outcomes and MVI. Finally, the number of MVI foci was not quantified on surgical specimens, and this information could have provided additional prognostic information since the finding of more than five foci seems to connote a dire prognosis (15).

In conclusion, with the present study, we support MVI as an important pathologic feature in a group of patients with PCa treated by the same surgeon and with pathological analysis performed by a single pathologist. After the follow-up period, 44.6% vs. 20.2% of the patients with and without MVI had biochemical recurrence respectively. Additionally, MVI along with serum PSA, clinical stage, capsular involvement and surgical margin status were independent predictors for recurrence when controlled for the other variables. This variable should be routinely used to help selection of patients to adjuvant treatments.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors from Sao Paulo present another manuscript on the age-old question: Does microvessel invasion (MVI) in the prostate offer any unique prognostic information? Is there any significance to the prostate cancer cell(s) that penetrate or abut the wall of vascular endothelial cells? Could this pathological finding lead to microscopic hematogenous dissemination of cells, leading to a biochemical recurrence, even in those patients with organ-confined disease?

The urologic literature contains numerous papers on this topic dating back at least 10 years

(McNeal et al.). There are noteworthy pitfalls when determining the true MVI within a particular radical prostatectomy specimen, such as the consistency of microvessel density (MVD) readings amongst individual pathologists and the quantitative ability to determine MVI. If this was standardized, the more relevant clinical question becomes whether MVI offers anything unique above the standard pathological and clinical parameters that are currently used to predict recurrence.

In this paper from Sao Paulo, the authors have evaluated 428 patients who had radical

prostatectomies performed by a single surgeon with a mean follow-up of 53 months. The pathology was read by a single pathologist, and although this can be considered a strong point, the question of variability of the MVD readings was not addressed in this paper. Of all the cases examined, only 11% were found to have MVI. What if there were several pathologists reviewing this blindly. Would that 11% be consistent?

The significant findings of this paper were that MVI had a 44.6% probability of disease recurrence vs. 20.2% among patients without MVI ($p < 0.001$). Unfortunately, there was no data presented in the paper indicating whether or not these biochemical recurrences were early or late when compared to the patients that did not have MVI. In addition, in an era when PSA doubling time has become an important surrogate prognostic indicator of metastatic disease and survival, there should have been some mention of this indicator. This type of information may have been meaningful, and should be explored, especially since there were

only 6 patients that developed metastatic disease in the study and there were no prostate cancer deaths. Interestingly, there was a lack of association with biopsy Gleason score, which has been determined by previous authors. So, are these findings meaningful, and will they change the patterns of care of our patients? Should this be done routinely, as the authors suggest, and discussed with patients in the postoperative consultation? "Sir, your have MVI, so, we now recommend...?"

Clearly, this needs more validation before we can use this to base adjuvant treatment decisions. I believe that we should be ordering tests only if we are going to act on the outcome. Otherwise, it is a research tool, and what is truly needed to answer this question is a randomized trial, which would demonstrate that adjuvant therapy in patients with MVI will improve the outcome, or have one as good as the MVI negative patients. Until then, its still research, and I commend the authors for trying to determine the true significance of this pathological finding (artifact?).

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EDITORIAL COMMENT

The importance of microvascular invasion (MVI) on prognostic information in urological malignancy is fully evaluated in the recent years (1,2). This paper presented the prognostic significance of MVI for biochemical recurrence after radical prostatectomy in 428 patients with prostate cancer. As the data were collected by a single surgeon and examined by a single pathologist, the analysis is consistent and reasonable. Multivariate analysis

demonstrated that 5 factors including serum PSA, clinical stage, capsular involvement, surgical margin status, and the presence of MVI were significant predictors for biochemical recurrence. As would be expected, the importance of MVI on prognostic impact for biochemical recurrence is not so high that other factors such as PSA and capsular involvement were still strong in this study population. For a given PSA value and/or presence or absence of capsular

involvement, how can MVI add prognostic information to these already known poor prognostic factors? The re-evaluation for the importance of MVI in more homogenous subpopulation might be more informative. Furthermore, in a clinical point of view, risk stratification or nomogram to identify the patients who should receive adjuvant therapy would need to be created. We still have an effort to confirm the importance of MVI for prognostic information for prostate cancer in a large, randomized, prospective study.

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Splenosis. A Diagnosis to be Considered

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ABSTRACT

The term splenosis applies to the autotransplanted splenic tissue resulting from seeding in the context of past splenic trauma or surgery. We report a 42-year-old man with a history of splenectomy observed for an incidentally found retrovesical mass thought to be an ectopic testicle. The abdominal laparotomy revealed multiple focuses of pelvic splenosis. As splenosis can be diagnosed through specific imaging studies one should always consider it in differential diagnosis of a mass discovered years after splenic surgery or trauma.

Key words: spleen; wounds and injuries; splenosis; bladder
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INTRODUCTION

Ectopic splenic tissue is a cause of incidentally found mass leading to diagnostic confusion. It can present as a congenital accessory spleen typically localized medially to the orthotropic spleen or as a mass detected several years after a splenic surgery or trauma. These implants, resulting from seeding, can mimic a neoplasm. However, specific diagnostic tests can confirm diagnosis and avoid unnecessary surgery.

In this paper we discuss a case of an incidental retrovesical mass in a patient with an absent left testicle that lead us to think of an ectopic testicle.

CASE REPORT

A 42 year-old male patient with a history of Behçet disease and a motor vehicle accident 20 years before resulting in emergent splenectomy, was referred due to an incidental retrovesical mass. A routine abdominal ultrasound detected a solid retrovesical

neof ormation independent from seminal vesicles. The CT scan confirmed a 3.7 x 2.5 cm mass (Figure-1).

No mass was identifiable on abdominal palpation or rectal exam. The left testicle was absent. IVU, transrectal ultrasound, and urethrocistocopy were normal. The hypothesis of an ectopic left testicle tumor emerged. Testis tumor markers (DHL, β -HCG and α -FP) were within normal range.

A pelvic MRI was ordered and revealed a nodular structure with 3.7 x 2.8 cm, morphologically ovoid, paramedially and superiorly to seminal vesicles, medially to the sigmoid colon and independently from these structures. Its lobulated contour with intermediate signal on T1, similar to muscle, and hyper signal on T2, superior to muscle and inferior to fat, were against a testicle but uncertainty on the nature of the lesion remained. An open abdominal laparotomy was performed. Multiple bluish-red nodules scattered through the pelvis involving both visceral and parietal peritoneal surfaces, suggested ectopic splenic tissue (Figure-2). The histological exam confirmed splenosis.



Figure 1 – CT scan. A 3.7 x 2.5 cm hyperdense retrovesical mass.

COMMENTS

Splenosis affects one to two thirds of patients submitted to splenectomy for trauma (1). Implantation from seeding is most frequently in serosal surfaces of small and large intestine, greater omentum, parietal peritoneum, mesentery, diaphragm

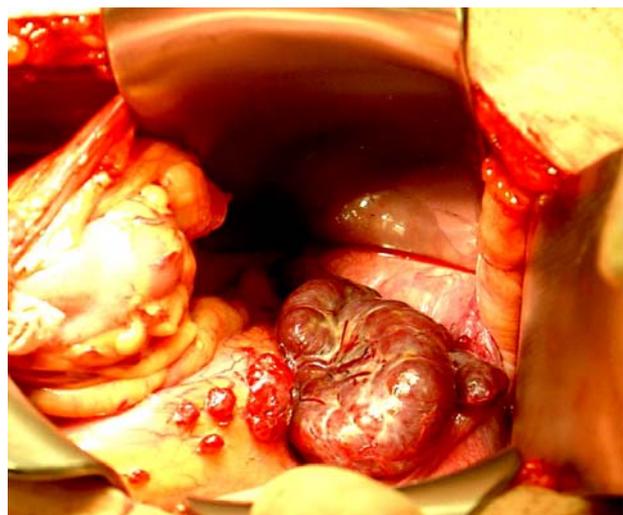


Figure 2 – Intraoperative picture revealing a large bluish-red mass and multiple small implants involving the peritoneum surface of pelvis suggesting ectopic splenic tissue.

undersurface and more rarely, in cases of severe trauma, intrahepatic or even intrathoracic (2,3).

Although splenosis can seldom present as a vague abdominal or testicular pain, intestinal obstruction from adhesions, GI bleeding and spontaneous rupture, it usually is an incidental finding during surgery, either laparoscopy or imaging (2).

When present as an incidental imaging mass it has been reported on to mimic renal, adrenal or abdominal tumors, metastases, lymphoma, endometriosis and ectopic testicles (1-4). Although usual imaging modalities (US, CT, MRI) are helpful to localize and determine the size, structure and relations with adjacent organs they are not specific.

If we had considered splenosis, signs of residual splenic tissue as the absence of Howell-Jolly bodies, siderocytes, Heinz bodies and pitted red cells on peripheral blood smear a could have been of help, but their presence is still possible due to less functioning splenosis tissue (2,3)

More specific and diagnostic studies using agents that are sequestered by reticuloendothelial tissue, like ^{99m}technetium sulfur colloid, ^{99m}technetium labeled heat-denatured autologous red blood cells or ¹¹¹In-labeled platelets scans (1,2) and recently ferumoxide-enhanced MRI (4) have been used.

In conclusion, all patients with a history of spleen surgery or trauma should consider the hypothesis of splenosis in differential diagnosis of a newly found mass.

CONFLICT OF INTEREST

None declared.

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Elective Appendicovesicostomy in Association with Monfort Abdominoplasty in the Treatment of Prune Belly Syndrome

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ABSTRACT

Objective: To evaluate the role of elective appendicovesicostomy in association with Monfort abdominoplasty to avoid urinary tract infection (UTI) and renal damage in the post-operative follow-up of patients with prune belly syndrome.

Materials and Methods: We followed 4 patients operated in our institution (UNIFESP) (Monfort, orchidopexy and Mitrofanoff) and compared them to 2 patients treated similarly, but without an appendicovesicostomy, in a second institution (UFBA). We evaluated postoperative clinical complications, UTI and preservation of renal parenchyma. Patients were followed as outpatients with urinalysis, ultrasonography (US) and occasionally with renal scintigraphy.

Results: Mean follow-up was 23.5 months. Immediate post-operative course was uneventful. We observed that only one patient with the Mitrofanoff channel persisted with UTI, while the 2 patients used as controls persisted with recurrent pyelonephritis (> 2 UTI year).

Conclusion: Our data suggest that no morbidity was added by the appendicovesicostomy to immediate postoperative surgical recovery and that this procedure may have a beneficial effect in reducing postoperative UTI events and their consequences by reducing the postvoid residuals in the early abdominoplasty follow-up. However, we recognize that the series is small and only a longer follow-up with a larger number of patients will allow us to confirm our suppositions. We could not make any statistically significant assumptions regarding differences in renal preservation due to the same limitations.

Key words: bladder; prune belly syndrome; surgical procedures, operative; urinary tract infections

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INTRODUCTION

Prune belly syndrome occurs once in 35,000 live births and consists of a triad of deficient abdominal wall musculature, intra-abdominal testes and dilated urinary tract. Extensive urinary tract reconstruction (cystoplasty, ureteroplasty and reimplantation) has moved up to more conservative approaches such

as clean intermittent catheterization (CIC) aiming to avoid residual volumes. Abdominoplasty plays a role not only in improving cosmetics but also in ameliorating bladder and intestinal emptying.

We adopted in our institution the concept of performing elective appendicovesicostomies in association with the Monfort abdominoplasty and orchidopexy. We believe that providing an outlet channel

adds little morbidity to the surgical procedure itself and brings a very beneficial mechanism of residual volume control. We hypothesized that by doing so we could be able to reduce the number of UTI and new scars per year in comparison to the classical strategy of watchful waiting. We believed as well that, in some case, we would be able to avoid the secondary need of urethral CIC, which can be a difficult issue due to the high sensitivity of the urethra.

We evaluated our concept of elective appendicovesicostomy in association with the Monfort abdominoplasty and orchidopexy with the classical strategy of abdominoplasty and orchidopexy only, by means of a retrospective comparative study involving 2 Brazilian institutions to answer this question.

MATERIALS AND METHODS

We reviewed the medical records of boys with prune belly syndrome treated in 2 centers from 1999 to 2004. We performed 6 Monfort abdominoplasties with patients ranging from 1 to 7 years (mean 3.5 years) at surgery. Antenatal diagnoses were possible in three patients and a fetal obstetric procedure was attempted in two cases (1 bladder puncture and 1 vesicoamniotic shunt). One patient developed initial respiratory distress while the others were born without other complications.

Urological investigation at the time of treatment identified bladders with increased capacity and hypotonic detrusor function. Half of the patients had massive vesicoureteral reflux (VUR). All patients presented recurrent symptomatic UTI. Bowel constipation was a rule except for one patient.

The standard surgical procedure consisted of classical Monfort abdominoplasty and open orchidopexy and was conducted in 4 cases in our institution and in two cases in the associated university (Table-1). Patients operated in our center additionally received the appendix implanted in the bladder dome after removal of the urachal diverticulum (Figure-1). A cystostomy tube was left for 3 weeks and after that the patient, and family, was trained by an urotherapist nurse to perform intermittent catheterization 4 times a day (Figure-2).

Patients were followed as outpatients. They were monitored with urinalysis to check for UTI and with US for upper urinary tract evaluation. Once a year the patients underwent a voiding cystogram, renal scintigraphy and, occasionally, an urodynamic study.

RESULTS

Early postoperative course was uneventful. Patients with the Mitrofanoff channel performed CIC initially 4 times a day but subsequently were oriented



Figure 1 – The appendix being implanted in the bladder dome after removal of the urachal diverticulum.



Figure 2 – Abdominal wall aspect after 3 weeks of surgery.

Table 1 – Clinical patient data.

Patient	Institution	Antenatal Diagnosis	Antenatal Diversion/Procedure	Born	Urodynamics	Voiding Cystogram	DMSA	Symptomatic UTI	Bowel Function/Constipation
HRSS	UNIFESP	No	No	39 weeks	Increased bladder capacity, hypotonic bladder	No VUR	No	1 to 2 episodes/year	Mild
RELT	UNIFESP	Yes	Yes (bladder puncture)	34 weeks	Increased bladder capacity, hypotonic bladder	Bilateral VUR	RK 60%, LK 40%	Recurrent pyelonephritis. Treated as inpatient	Massive
LVS	UNIFESP	Yes	Yes (vesicoamniotic shunt)	36 weeks, respiratory complications	No	No VUR	RK 43%, LK 57%	> 2 episodes/year	Mild
GRC	UNIFESP	Yes	No	38 weeks	No	No VUR	No	Recurrent pyelonephritis	Massive
MVAC	UFBA	No	No	38 weeks	No	VUR IV right / III left	No	1 to 2 episodes/year	Mild
MNR	UFBA	No	No	40 weeks	No	VUR IV left	RK 95%, K 5%	Recurrent pyelonephritis	No

UNIFESP = Federal University of Sao Paulo; UFBA = Federal University of Bahia; VUR = vesicoureteral reflux; RK = right kidney, LK = left kidney.

to catheterize their bladder only after a spontaneous micturition. Residual volume reduction was seen in three of four patients and CIC frequency could be reduced. Two patients had documented residual volume and therefore maintained regular catheterization over 2 times a day. One patient did not perform any CIC and another one did it only once a day. The clinical follow-up for this group of patients was satisfactory and 3 of them did not have any more clinical UTI. The patient who persisted with mild clinical UTI remained with VUR and was referred to an anti-reflux surgery.

The two patients of the other group initially maintained high residual volumes but one recovered progressively as he started voiding better. Clinically both these patients had recurrent pyelonephritis (more than 2 UTI a year).

All patients felt an improvement in constipation and were very satisfied with the final cosmetic appearance of the abdominal wall.

We could not correlate renal damage with the surgical procedure. Concerning the vesicoureteral reflux, one patient is still waiting for surgery, one has been previously operated and the other has reflux into a nonfunctional kidney and nephrectomy is being considered. Present follow-up is 23.5 months (Table-2).

COMMENTS

The overall prognosis of prune belly syndrome is poor, with more than 20% of extreme cases being stillborn. Renal failure will develop in approximately 30% of survivors during childhood and adolescence. Early detection of urinary infection or renal deterioration can be done by close surveillance enabling early recognition of bladder drainage abnormalities, which are the main source of complications.

Table 2 – Clinical post-operative evolution.

Patient	Age at Surgery	Elective Appendicovesicostomy (plus Monfort and orchiopexy)	Ureteral Reimplantation	CIC / Daily Frequency	Residual Volume	Complications/ Symptomatic UTI	Bowel Function/ Constipation
HRSS	7 years	Yes	No	No	No	No	Significant improvement
RELT	1.5 years	Yes	No	Yes / 4	Yes	Episodic UTI: anti-reflux surgery proposed	Improvement
LVS	3.2 years	Yes	No	Yes / 2	Yes	No	Significant improvement
GRC	4 years	Yes	No	Yes / 1	No	No	Significant improvement
MVAC	5 years	No	Yes / Cohen technique	No	No	Recurrent pyelonephritis / reflux nephropathy / hypertension	Improvement
MNR	1 year	No	No	No	Yes	Recurrent pyelonephritis	Improvement

Reduction cystoplasty and extensive tailoring of the ureters and reimplantation have been advocated in an attempt to improve drainage but adequate emptying can in fact be obtained with clean intermittent catheterization. The abdominal wall defect has long been regarded as a purely cosmetic disability and managed by elasticized corset-like body stocking undergarments, but clinical results with the Monfort wall plasty emphasized improvements in self-esteem, bowel function and marked reduction in post-void residual urine (1). Smith et al. reported a decrease in post-void residual volumes in 7 patients treated by the Monfort abdominoplasty without concomitant urinary tract reconstruction from 40% of bladder capacity preoperatively to 14.3% postoperatively.

Another argument in favor of reconstructing the abdominal wall is the beneficial effect on spinal stability. The prevalence of spinal deformities, particularly those related to scoliosis, in prune belly syndrome might be secondary to a chronic imbalance in spinal musculature and there is evidence that abdominal wall strengthening constitutes an important aspect in the restoration of overall trunk muscle function and stability (2).

The Monfort abdominoplasty enables an effective increase in the thickness of the anterior wall and rapidly gained popularity after its introduction to the medical community (3,4).

Other techniques have been proposed as alternatives to the Monfort abdominoplasty. Furness et al. reported on an extra peritoneal plication technique which obviated the need for a fascial incision and/or entrance into the peritoneal cavity and presented adequate cosmetic results in 13 patients (5). Although this method consists of an extra peritoneal approach, only 5 patients from the series were treated without celiotomy, since most patients required at least an open orchidopexy at the time of the abdominoplasty.

We believe that the Monfort procedure is "the gold standard" technique to reconstruct the abdomen. We perform the Monfort procedure routinely for full-blown syndrome at the time of transabdominal orchidopexy in early infancy. The appendicovesicostomy procedure is a straight-forward procedure once the abdominal wall is open and the bladder prepared after removal of the urachal diverticulum. We admit,

however, that controversy exists regarding the true advantage of early post-operative intermittent catheterization as defended in our study.

In our series, we were able to compare 4 patients who started urinary catheterization immediately after abdominoplasty 4 times/day through a Mitrofanoff channel with 2 patients who were not provided with an outlet channel. All patients presented recurrent UTI and bowel constipation pre-operatively. We recognize that due to the small number of patients, no definitive conclusion can be taken but we were able to identify some trends in the clinical evolution of these patients. Considering UTI as a clinical parameter, we observed that patients in the first group had significantly less UTI than patients in the second group, which had persistence of recurrent pyelonephritis (more than 2 a year). However the presence of vesicoureteral reflux is a second factor that also contributes to UTI occurrence besides post-void residuals and in cases in which both factors occur we recognize is not possible to attribute the influence of each separately. The beneficial aspects of abdominoplasty were visible in both groups, consisting of improvement in bowel habits and reduction of the residual volume. Patients with elective Mitrofanoff showed progressive reduction of residual volume and at the last follow-up only two of them needed objectively post-void catheterization (more than 40% of the capacity). In the other group, one of the two also did not present residual volume. This result suggests that abdominal wall reconstruction itself is responsible for improvement in bladder emptying and that an elective Mitrofanoff is advantageous, only during the accommodation period, for 50% of the patients and essential, for much longer periods, for the other 50%.

If one considers that pyelonephritis is an important risk factor for renal scars in children less than 5 years of age, it seems logical to consider ways to minimize such risk. The popularization of CIC and catheterizable stomas in pediatric urology helped us to learn about the advantages and special cares and needs of patients and families and also about the complications of appendicovesicostomy. One could argue that when we provide a Mitrofanoff channel for every patient with prune belly we are probably overtreating many of them. This is probably true and our

series suggests that this might have happened in half of the cases. On the other hand, the aggressive treatment of residual volume may have a role in renal function preservation although this could not be proved in this short series. We agree that the persistence of vesicoureteral reflux also might have been an important factor contributing to postoperative pyelonephritis and this should be considered when evaluating overall response to the treatment we are proposing (6).

We should note that an appendicovesicostomy is a simple surgical step when one is already reconstructing the abdominal wall but it is certainly more complicated if performed later on.

Another beneficial aspect of routine early abdominoplasty is the possibility of performing concomitant orchidopexy. Recent advances in the treatment of fertility support the idea that many patients with the prune belly syndrome may ultimately be fertile and therefore treated. Repair in infancy generally allows successful placement of the testes into the scrotum without division of the spermatic vessels which is obviously facilitated by the abdominal incision. In our series, all testes were easily brought to the scrotum and showed no evidence of retraction or shrinkage in the present follow-up.

CONCLUSION

In conclusion we believe that treatment of the prune belly syndrome is evolving and if one is interested in the functional aspects of the urinary tract our concept of early abdominal bladder emptying is appealing. As seen in this short series, no morbidity was added to the first group compared to the classical approach of abdominal wall reconstruction and orchidopexy. Our data suggests beneficial effects in reducing post-operative UTI events in the elective Mitrofanoff group of patients. We recognize, however, that the series is small and only a longer follow-up with larger number of patients will allow us to confirm our suppositions. We admit that this approach is novel and it is still in investigation in our Department and we recognize the opinion of others regarding the standard approach which is still abdominoplasty alone and a Mitrofanoff channel in

more selected cases. However this “no risk at all strategy” with little increase of morbidity during the Monfort abdominoplasty is definitely an argument to propose this different approach.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Parallel to its main characteristics, the Prune Belly Syndrome (PBS) is also known for a variable presentation among the patients, as well as the lack of correlation between the degree of abdominal laxity and urinary tract involvement. Also, the intensity of dilatation and dysplasia of one kidney and its ureter is not the same as that of the contralateral unit. The presence of vesicoureteric reflux (VUR), and the capacity of the bladder to empty itself adequately are other variables that have to be considered when planning the treatment of these patients.

In this work, the authors present their experience with 5 patients in whom a Mitrofanoff channel was added as a means for easy catheterization, when abdominoplasty and orchiopexy were performed. The concept of intermittent bladder catheterization in PBS patients is interesting, since several, but surely not all of them, have significantly enlarged and hypotonic bladders, with post-void residuals, that are associated to urinary tract infection (UTI). Nevertheless, the presence of VUR to a dilated ureter, sometimes associated to a kidney with already limited function, is probably more important in the cause and recurrence of pyelonephritis. In the group of patients described, it seems that persistence of VUR was more important for the recurrence of UTI and pyelonephritis than the lack of the Mitrofanoff channel.

Not mentioned by the authors, the comprehensive surgical treatment, proposed by Woodard almost 30 years ago, includes the simultaneous orchiopexy and abdominoplasty with the reconstruction of the urinary tract, according to individual needs: the non-functioning kidneys and its ureters are removed, the very dilated and/or refluxing ureters are tailored and reimplanted and the very enlarged bladders are partially reduced in size, with removal of their non-contractile domes and urachal diverticulum (1). With

this procedure, the anatomical conditions of the urinary tract that predispose further renal injury due to pyelonephritis are significantly reduced. In our experience of 32 patients treated comprehensively without primary diversion, 20 (including 4 without bladder reduction) had normal postoperative voiding, without residuals, and 9 presented a hypocontractile bladder, but had adequate emptying achieved with scheduled voiding associated to Credé's and Valsalva's maneuvers. Only 3 patients had significant postvoid residuals, requiring either intermittent catheterization or secondary vesicostomy. Furthermore, recurrent asymptomatic bacteriuria was observed in only 4 children, including 2 undergoing intermittent catheterization, while renal function deteriorated in only 2 patients (2).

It is our opinion that the comprehensive surgery efficiently prevents UTI and pyelonephritis in PBS patients not only by reducing urinary stasis in the bladder and ureter, but also by eliminating the VUR. The addition of a Mitrofanoff channel to the procedure, on an individual basis, may help on the long run the reduced number of patients whose bladders have significant and irreversible voiding malfunction. However, the correct preoperative identification of such patients is still matter of debate.

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EDITORIAL COMMENT

One of the most important problems related to the Prune Belly syndrome is regarding the urinary stasis and incomplete bladder emptying, both predisposing to repeating conditions of acute pyelonephritis and loss of renal function. The reduction of postvoid residuals can be obtained with reduction cystoplasty at the bladder dome, sphincterectomy, and ureteral tailoring with reimplantation, besides abdominoplasty. Clinical measures can be added such as the Valsava and Credé maneuvers and, finally, intermittent catheterization (made difficult due to the normal sensibility of the urethra). As an additional preventive measure the authors propose a systematic construction of abdominal stoma in association with the Monfort abdominoplasty and present a comparative study in 6 cases, insufficient for significant conclusions, but justifiable due to the low incidence of the syndrome. A lower incidence of pyelonephritis was obtained in the diverted group and a routine incorporation of the abdominoplasty procedure was suggested.

On reference 1 in the manuscript, the voiding function was studied in 12 patients before and after abdominoplasty. The questionnaires answered showed a subjective increase in voiding, continence, vesical plenitude sensation and urinary flow parameters. However, the urodynamic parameters, bladder capacity and maximum detrusor pressure did not change. Even though the mean residual volume dropped from 40.3% to 13%, no patient required intermittent catheterization and the incidence of UTI dropped approximately 80% in all patients. Such data show a direct cause implication of

abdominoplasty over the micturition quality. Dénes et al. (1) reported longitudinal abdominoplasty and urinary reconstruction in 32 patients with a mean postoperative follow up of 5 years. Twenty patients progressed with normal voiding without residual urine, 9 were compensated with Credé and Valsava maneuvers, 2 were submitted to catheterization and 1 to a vesicostomy. Renal function worsened in only 2 patients. The mentioned works included heterogeneous samples, both in relation to the severity of the cases and to the urinary reconstruction performed, making it difficult adequate comparisons. However, they suggest cutaneous derivation routinely associated to abdominoplasty, as proposed in the present work, even though with little change in morbidity, seems to mean overtreatment for the majority of the patients. In the lack of a well defined criteria, the preoperative selection of cases with compromised renal functions and high residual volumes, may contribute for a more rational and precise indication of the Mitrofanoff principle. Another pertinent consideration would be the convenience of the treatment of high degree reflux together with abdominoplasty aiming at avoiding future re-intervention besides contributing to urinary infections control.

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Urogenital Involvement in the Klippel-Trenaunay-Weber Syndrome. Treatment Options and Results

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ABSTRACT

Objective: Klippel-Trenaunay-Weber syndrome (KTWS) is a congenital condition characterized by vascular malformations of the capillary, venous and lymphatic systems associated to soft tissue and bone hypertrophy in the affected areas. This syndrome may involve bladder, kidney, urethra, ureter and genitals. We report the treatment of 7 KTWS patients with urogenital involvement.

Materials and Methods: From 1995 to 2005, 7 patients with KTWS were evaluated and the charts of these patients were reviewed.

Results: Patients' median age was 19-years (range 4 to 46-years) and only 1 was female. The clinical presentation included genital deformities in 3 cases, hematuria in 2 and urethrorrhagia in 2, one of which associated with cryptorchidism and phimosis. Three patients had an association of pelvic and genital malformations, including 2 patients with hematuria due to vesical lesions and 1 patient with left ureterohydronephrosis due to a pelvic mass. Two patients had urethral lesions. Treatment included endoscopic laser coagulation for 1 patient with recurrent hematuria and 1 patient with urethrorrhagia, pelvic radiotherapy for 1 patient with hematuria and circumcision in 2 patients with genital deformities. One patient required placement of a double-J catheter to relieve obstruction. Hematuria and urethrorrhagia were safely and effectively controlled with laser applications. Circumcision was also effective. The patient treated with radiotherapy developed a contracted bladder and required a continent urinary diversion.

Conclusions: Urogenital involvement in patients with KTWS is not rare and must be suspected in the presence of hematuria or significant cutaneous deformity of the external genitalia. Surgical treatment may be warranted in selected cases.

Key words: Klippel-Trenaunay-Weber syndrome; urogenital system; hematuria, lasers, bladder

Int Braz J Urol. 2006; 32: 697-704

INTRODUCTION

Klippel-Trenaunay-Weber Syndrome (KTWS) is a rare congenital syndrome characterized by vascular malformations of the capillary, venous and lymphatic systems associated to soft tissue and bone hypertrophy of an affected lower limb. These alterations are frequently misdiagnosed as

simple hemangiomas, which have a different clinical behavior (1).

Historically, Klippel and Trenaunay described the first case of KTWS in 1900 and in 1907 Weber described similar cases. They believed that the syndrome was secondary to large congenital arteriovenous fistulae, causing hypertrophy of the affected limb (2). Recently, Tian et al. identified an

angiogenic factor, termed VG5Q, that when over expressed due to mutations on its gene, causes increased angiogenesis. This is accepted as the molecular pathogenic mechanism of KTWS (3).

There is considerable variability in the terminology for these similar syndromes. The diagnosis of the Klippel-Trenaunay Syndrome should be applied to cases without arteriovenous fistulae, while Weber or Parks-Weber Syndrome is more appropriate for cases with arteriovenous fistulae (4). Since the differentiation between the two conditions is only possible by means of histopathological, radiological and/or genetic evaluation, we employ the name Klippel-Trenaunay-Weber Syndrome, as recommended by other authors (5).

Involvement of genitourinary organs is not rare in patients with KTWS. The bladder is estimated to be affected in 2.3% to 6% of the cases (1). Hematuria is usually the initial clinical manifestation (1,2). The urethra, external genitalia, kidney and ureter may also be involved (1).

In this study, we report our experience with seven patients with KTWS and urogenital involvement.

MATERIALS AND METHODS

We retrospectively reviewed the records of seven consecutive patients (6 men and 1 woman) evaluated over a period of 10 years, who were referred to urological evaluation with a previously established diagnosis of KTWS. The criteria employed for the KTWS diagnosis were the typical clinical and physical features.

Urological assessment and management varied according to the patient's complaints and affected organs. A focused history and physical examination was performed in all cases. Laboratorial and imaging studies were obtained according to clinical presentation.

RESULTS

The bladder and external genitalia were the most commonly affected organs in our series. Sym-

ptoms presented were penile deformity in three patients, recurrent gross hematuria in two, urethral bleeding in one and phimosis and cryptorchidism in one. One patient had both penile deformity and unilateral hydronephrosis, due to entrapment of the bladder and distal segment of the left ureter secondary to a large pelvic malformation. The patients' data, urogenital structures involved and urological management are depicted in Table-1.

Case 1: A 46-year-old man had a history of gross hematuria since childhood. He had a typically enlarged right leg and penile varicosities. He underwent cystoscopy elsewhere at the age of 21 revealing a large hemangiomas bladder lesion. He was treated with external beam radiotherapy, and developed actinic cystitis that evolved to a contracted bladder with lithiasis. A continent diversion with a sigmoid segment was performed 11 years later, and he remained free of hematuria and other symptoms for the following 14 years.

Case 2: A 4-year-old boy presented an enlarged right leg and a lymphedematous enlarged penis and preputial skin that caused voiding difficulty. He was previously treated elsewhere by inguinal lymphatic-venous diversion and circumcision. Penile enlargement and deformity persisted but the voiding symptoms resolved after the foreskin was partially removed. He was managed with further surgical reduction of the lymphedematous tissue of the penis with significant aesthetical improvement.

Case 3: A 5-year-old boy with sickle cell anemia presented an extremely enlarged right leg, penile deformity due to hemangiomas varicosities, lymphedema (Figure-1) and a palpable pelvic mass. Abdominal ultrasound revealed left ureterohydronephrosis and a pelvic mass involving the bladder. An abdominal CT scan showed a large bladder lesion extending to the left pelvic wall (Figure-2). Cystoscopy demonstrated an intensely vascularized bladder lesion that infiltrated most of the bladder dome and left wall, including the left ureteral orifice. The penile deformity was managed with surgical removal of the hemangiomas varicosities and a double J catheter was placed to drain the left kidney. A laparoscopy was performed simultaneously to evaluate the pelvic mass, which was shown to extensively

Klippel-Trenaunay-Weber Syndrome

Table 1 – Urogenital involvement in Klippel-Trenaunay-Weber syndrome and the respective treatment.

Case	Age	Gender	Race	Involved Organs	Symptoms	Urological Management
1	46	Male	Black	Penis, bladder	Recurrent gross hematuria	Pelvic RDT and continent diversion
2	4	Male	White	Penis	Voiding difficulty, penile deformity	Postectomy
3	5	Male	White	Penis, bladder, left ureter	Pelvic mass, left ureterohydronephrosis, penile deformity	Double J catheter and removal of penile varicosities
4	15	Male	White	Urethra	Urethral bleeding	Holmium laser ablation
5	25	Female	Black	Bladder, vulva	Recurrent gross hematuria, vulvar deformity	Nd:YAG laser ablation
6	5	Male	White	Penis, urethra	Phimosis, cryptorchidism and urethral bleeding	Postectomy and orchiopexy
7	5	Male	White	Penis	None	Observation



involve the bladder and rectum-sigmoid colon, and was considered irresectable. The patient has been managed conservatively in the last two years with periodic changes of the ureteral catheter, but progressive left renal deterioration occurred due to increasing growth of the pelvic mass. He has also presented recurrent penile varicosities and urethral bleeding that has been managed conservatively.

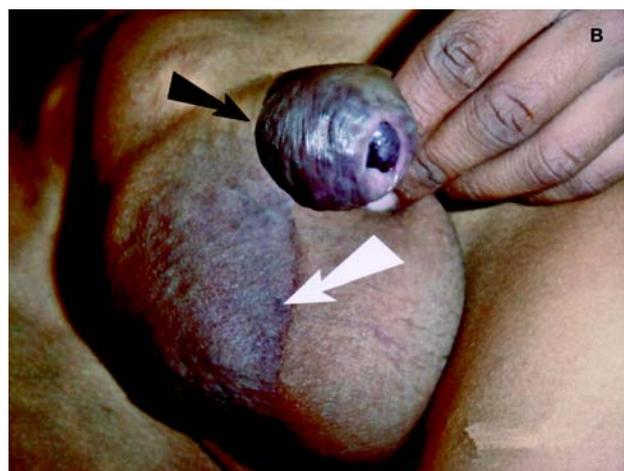


Figure 1 – Five-year-old boy (case #3) with Klippel-Trenaunay-Weber syndrome. A) Note massive soft tissue hypertrophy and cutaneous vascular malformations of the right leg, perineum and left foot toes. Three left toes amputation were performed. B) Detailed view of penis and scrotum, showing vascular malformation of preputial skin (black arrow) and glans, and right hemiscrotum (white arrow).

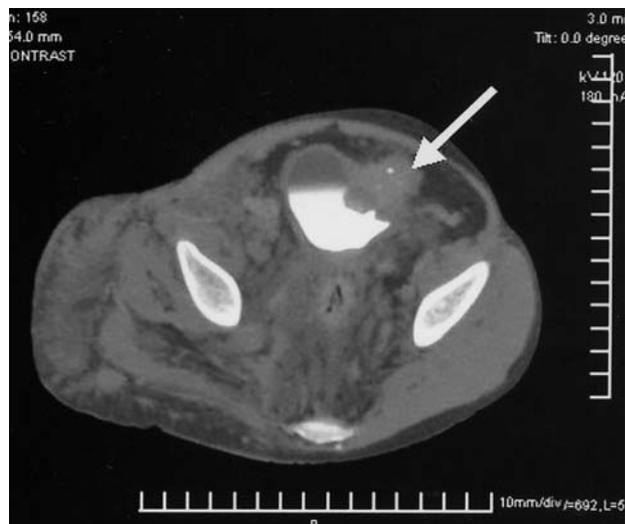


Figure 2 – Pelvic CT scan (case #3) with intra-vesical contrast medium showing a large lesion involving the left anterior bladder wall (white arrow).

Case 4: A 15-year-old boy presented an enlarged left leg and buttock and a history of intermittent urethral bleeding. Urinary tract sonography was normal. Cystoscopy revealed active bleeding from distal urethral varicose veins, but no bladder lesions. He was treated with Holmium laser application in the urethral varicosities. The laser was used with 6 W and a 400 nm fiber. Laser was applied in contact with the urethral mucosa until vascular sclerosis was achieved. A urethral catheter was left for 7 days. After 14 months follow-up, the patient remained free of urethral bleeding.

Case 5: A 25-year-old woman had a diagnosis of KTWS since the age of five. Her medical history included left colectomy at the age of 15, due to life-threatening enterorrhagia caused by a large pericolonic vascular malformation. She also had a history of sporadic episodes of gross hematuria that were treated conservatively with bladder irrigation, endovenous epsilon amino-caproic acid and occasional blood transfusions. She was referred to our hospital after unsuccessful treatment of recurrent massive hematuria requiring multiple blood transfusions. Physical examination revealed hemangiomas and hypertrophy of the perineum and entire left inferior limb. A suprapubic mass was palpable. Abdomi-

nal CT scan revealed diffuse pelvic vascular lesions, involving bladder wall, peri-rectal and paravesical spaces. Cystoscopy revealed a large, elevated and irregular lesion with hemangiomatous features that involved 60% of the bladder surface on the left, posterior, anterior and dome walls, with well-defined borders and many bleeding sites. The lesion was treated with a continuous pulse Nd:YAG laser, using a 0.6 mm fiber. The tip of the fiber was positioned 5 mm from the bladder surface. Total energy delivery was 3,000 joules in 90 minutes. Bleeding ceased immediately and the bladder catheter was removed on the first postoperative day. After a follow-up period of 14 months, the patient remained free of hematuria.

Case 6: A 5-year-old boy presented enlargement of both hands and left lower limb. He had right cryptorchidism, phimosis and a history of a single episode of urethrorrhagia. The testicle was palpable on the inguinal canal. Many small veins could be seen under the penile skin. Orchiopexy and circumcision were effective, but subcutaneous veins made the dissection of the preputial skin more difficult, requiring ligation of veins and the use of a compressive dressing. At urethrocystoscopy a small vascular malformation was found in the prostatic urethra, with no signs of recent bleeding.

Case 7: A 5-year-old boy was referred for evaluation due to a mild penile and scrotal enlargement associated with a significant enlargement of the left leg. He was otherwise asymptomatic. His pelvic CT scan showed an infiltrating mass in the left buttock, posterior perineum and genital area. The bladder and urethra were not affected and he was managed conservatively.

COMMENTS

Urogenital involvement in patients with KTWS is not uncommon and may present with different manifestations. Bladder involvement is estimated to occur in 2.3% to 6% of the patients, penoescrotal vascular malformations in 8.5% and vaginal or vulvar in 9.5% of the patients (1). Cases of kidney, renal artery and ureteral involvement have rarely been reported (1,6-8). Our series is in accor-

dance with these numbers, with a prevalence of bladder and genital involvement and one patient with ureteral obstruction associated with a massive pelvic vascular malformation.

In cases of extensive cutaneous lesions of the genitals, lower extremities and buttocks, retroperitoneal and urinary tract involvement should be suspected and radiological evaluation with CT scan or MRI is recommended (1). Hematuria and urethral bleeding are also indications for urological evaluation. Bladder and urethral lesions may be confirmed with cystoscopy. In the bladder, they are usually reddish-blue and may be pedunculated, sessile, lobulated or flattened, and are frequently located at the anterior wall or dome (1). Biopsies can lead to massive bleeding and are not recommended.

Initial treatment of gross hematuria in these patients is conservative, with bladder irrigation. Antifibrinolytic agents as epsilon amino-caproic or tranexamic acid can be used (9). In one of our patients (case 5), epsilon was ineffective. Recurrent or life-threatening hematuria demands specific treatment. Partial cystectomy used to be the standard treatment but carries significant morbidity (10,11). Selective embolization of the internal iliac arteries may also be employed, but recurrence due to rapid development of collateral circulation and bladder or prostate infarction has been described (12). Radiotherapy is another therapeutic modality, but only temporary beneficial results are expected, while the morbidity can be excessive (13). In Case 1, radiotherapy resulted in actinic cystitis and loss of a functional bladder, requiring urinary diversion.

The first report of Nd:YAG laser treatment of bladder hemangiomas associated with KTWS was made by Smith and Dixon in 1984 (14). Since then, a few cases have been described, with good results (12,13,15,16). In 1990, Smith reported 13 cases of patients with bladder hemangiomas who underwent treatment with Nd:YAG laser, 6 of whom with KTWS (2). Since then, endoscopic treatment with Nd:YAG laser has been advocated as the gold standard procedure for bladder hemangiomas. In Case 5, the endoscopic approach was used with some technical aspects differing from those described in the literature. We used saline solution to fill the bladder as opposed

to CO₂ utilized by Kato (12). Since the lesion was very large, our strategy was to initially coagulate the margins of the lesions, in order to decrease blood supply to the bleeding sites. Next, we applied the laser directly to the central areas with large veins, which resulted in bleeding that was easily controlled by applications in the base of the veins. The immediate and mid-term results were excellent, without recurrence of bleeding for more than one year.

The trigone and bladder neck are reported to be rarely involved, but two of our patients (cases 3 and 5) had involvement of the posterior bladder wall and trigone, including obstruction of the left ureteral orifice in Case 3. This is the fourth reported case of KTWS causing hydronephrosis (1,8). Furness et al. described the treatment of one of such cases with ureterolysis. In this case, due to extensive vesical, retroperitoneal and pelvic involvement, the patient was managed conservatively with insertion of a ureteral Double-J catheter to preserve the renal function.

Urethral bleeding is extremely rare in patients with KTWS. We found only one case in the literature, which was treated with excision of the affected urethral segment and full-thickness skin graft. Other cases of urethral bleeding caused by hemangiomas or vascular malformations and not associated to KTWS were treated by excision, Nd:YAG or KTP laser (17,18). Three of our cases had episodes of urethral bleeding. In Case 4, it was controlled with Holmium laser applications on the varicose veins, which to our knowledge represents the first successful report of such treatment. Case 6 had only one self-limited episode of urethral bleeding, and urethroscopy revealed a small prostatic urethra lesion that was not treated. In case 3, the episodes have been mild and sporadic, and no therapy was needed.

Genital lesions are usually managed conservatively. Ulcerations or small bleeding areas are treated with topical antibiotics and compressive dressings. Significant deformity of the penis can be managed with postectomy when necessary. It is usually a safe procedure but may require surgical revision, as occurred in Case 2. Since vascular malformations are not hemangiomas, treatments with steroids, sclero-

therapy and radiation are not indicated (1). Phimosi can be managed by circumcision. However, careful dissection is necessary, due to the possibility of anomalous enlarged subcutaneous veins, as seen in case 6.

KTWS lesions are not malignant but can have a malignant behavior according to their size and location, as seen in Case 3. Life expectancy for patients with KTWS is not determined in the literature, but adulthood can be reached and many cases of successful pregnancy and delivery have been reported (19). Patients with KTWS must have adequate support and treatment. Vascular and plastic surgeries can ameliorate aesthetic aspects, improving quality of life (17,20). Urologists can have an important role in the care of these patients and must be prepared for that.

CONCLUSIONS

Urogenital involvement in the Klippel-Trenaunay-Weber Syndrome must be suspected when hematuria or urethral bleeding occurs or when extensive cutaneous lesions of the pelvis, genitals, lower extremities and buttocks are present. Imaging studies and urethroscopy confirm the diagnosis. Genital cutaneous malformations may be treated surgically when associated to severe deformity. Hematuria and urethrorrhagia are often managed conservatively, but life-threatening or recurrent episodes should be treated endoscopically. Laser seems to be a good therapeutic option for bleeding vesical or urethral lesions, but the best type of laser for this purpose is yet to be determined.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The Klippel-Trenaunay syndrome (KTS) is an unusual congenital anomaly. It causes symptoms due to genitourinary system involvement in approximately 6% of the cases (1).

The most feared urological complication is recurrent gross hematuria due to bladder involvement, which could be quite difficult to manage. The paper has a substantial number of KTS patients with genitourinary involvement but in this series none of the patients suffered from recurrent bleeding following treatment, which may not always be the case. The authors described 2 cases of gross hematuria, one case was initially treated with radiotherapy, which caused contracted bladder; it is not the recommended treatment in such patients. In the second case a massive hemangiomatous lesion was

successfully treated with Nd: YAG laser in a single session. Another case, which had extensive bladder hemangiomatous lesions, did not cause any bleeding but caused obstruction to the upper tracts. It was managed by insertion of double J stent through the lesion, which could be technically demanding and lead to local irritation, and precipitation of hematuria. The rest of the cases were dealt straightforwardly.

Most publications regarding genitourinary manifestations in Klippel Trenaunay syndrome comprise of individual case reports and as the presentation is variable there is no gold standard in treatment. Amongst many options available, Nd: YAG laser has been most commonly and successfully employed as the first line treatment for bleeding from these hemangiomatous lesions. Recently a newer

treatment with systemic alpha-interferon has been used in a single patient with problematic recurrent hematuria with good short-term results (2).

These patients need long term and close follow up. Any benefit of treating bladder and urethral lesions prophylactically remains to be established. However, the lesions in Klippel Trenaunay syndrome are not true hemangiomas but it may be worthwhile to evaluate any long-term role of endothelial cell growth inhibitors like interferon alpha-2a in preventing bleeding.

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Pudendal Nerve Latency Time in Normal Women via Intravaginal Stimulation

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ABSTRACT

Introduction & Objectives: Studies of motor conduction for the efferent functional assessment of the pudendal nerve in women with pelvic dysfunctions have been conducted through researching distal motor latency times. The transrectal approach has been the classic approach for this electrophysiological examination. The objective of the present study is to verify the viability of the transvaginal approach in performing the exam, to establish normal values for this method and to analyze the influence of age, stature and parity in the latency value of normal women.

Materials and Methods: A total of 23 volunteers without genitourinary pathologies participated in this study. In each, pudendal motor latency was investigated through the transvaginal approach, which was chosen due to patient's higher tolerance levels.

Results: The motor response represented by registering the M-wave was obtained in all volunteers on the right side (100%) and in 13 volunteers on the left side (56.5%). The mean motor latency obtained in the right and left was respectively: 1.99 ± 0.41 and 1.92 ± 0.48 milliseconds (ms). There was no difference between the sides ($p = 0.66$). Latency did not correlate with age, stature or obstetric history. The results obtained in the present study were in agreement with those found by other researchers using the transrectal approach.

Conclusion: The vaginal approach represents an alternative for pudendal nerve distal motor latency time, with similar results to those achieved through the transrectal approach. Normative values obtained herein might serve as a comparative basis for subsequent physiopathological studies.

Key words: *electrodiagnosis; pelvic floor; urinary incontinence; perineum; neurophysiology*

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INTRODUCTION

Somatic innervation of the female pelvic floor is basically represented by the pudendal nerve. The integrity of this nerve is important for the functioning of the skeletal musculature of this region, part of the mechanism that sustains pelvic structures and for anal and urethral sphincteric activity (1). This nerve is characterized by presenting sensitive and

motor fibers derived from the medullar segments S₂-S₄. Its inferior rectal and perineal ramifications play an important role in external anal and urethra sphincter innervations respectively (2).

Efferent functional neurological analysis is performed through measurement of motor conduction speed. This method requires access to 2 separate points of the same nerve for stimulation and registration, making its application on the pelvic floor difficult (3).

Thus, research on distal motor latency described by Kiff & Swash (4) became an alternative in the propedeutic of abnormalities of pudendal nerve motor function. The advantage lies in the need to stimulate only one point of the nerve. Registration can be made in the anal sphincteric musculature corresponding to the compound muscular potential of action or M-wave. These researchers also developed the St. Mark's pudendal electrode – a name given in honor of the institution where they worked (St. Mark's Hospital, London, UK). This is a self-adhesive electrode placed on the researcher's index finger at a fixed distance of 3 cm with bipolar electrodes for stimulation and registration places at the tip and base of the finger respectively (Figure-1). This method is used to investigate lesions of the pudendal nerve associated with dysfunctions in the pelvic floor. Patients with a previous history of obstetric rupture of the anal sphincter presented a higher risk of fecal incontinence when pudendal motor latency was higher than 2 milliseconds (ms) (5). A study in nulliparous patients and in the puerperium showed an extension of latency in the latter persisting for 5 years after vaginal delivery (6). A similar finding was found in women with stress urinary incontinence and concomitant genital prolapse (7). All these studies were conducted through stimulation and transrectal registration. A single previous study comparing the transrectal and transvaginal stimulation routes in the same normal volunteers showed the same findings (8). The present consensus suggests that the transvaginal approach is effective and useful (9), and it has the advantage of allowing greater tolerability by women due to their familiarization with regular gynecological exams.



Figure 1 – St. Mark's pudendal electrode stands out in the uroneurophysiology lab. Electrode of stimulation and registration sites, respectively, at the tip and base of the index finger. A distance of 3 cm separates the registration electrodes from the stimulation cathode.

MATERIALS AND METHODS

Following approval by the institution's Ethics Committee, a prospective study was performed on 23 normal volunteers. Their characteristics are described in Table-1. Women without significant genitourinary alterations were included, providing no previous history of extensive pelvic and vaginal surgery (including women who had already undergone cesareans or unilateral adnexal surgery), diabetes mellitus, renal insufficiency, alcoholism, hyperthyroidism, present and previous neurological alterations, interstitial cystitis, present urinary infection, voiding dysfunctions, pregnancy or use of a cardiac pacemaker.

Table 1 – Characteristics of the sample in relation to age, corporeal weight, stature and parity (mean \pm standard deviation).

	Age (years)	Stature (cm)	Parity	
			Vaginal Delivery	Total Parity
Mean	34.8 \pm 13.7	159 \pm 7	1.23 \pm 1.01	1.69 \pm 0.85
nterval	18-74	140-160	0-3	0-3
Number of Cases	23	23	14	24

Four channel Nihon-Kohden electroneuromyography equipment, model Neuropack sigma (Σ), was used to perform the examination.

The study was conducted with the volunteer in the lithotomy position. The St. Mark's pudendal electrode (Medtronic Functional Diagnostics A/S, Skovlunde, Denmark, model 13L4401) was attached to the researcher's index finger (Figure-1). In the 14 initial volunteers, the bilateral research was performed only with the right hand of a right-handed researcher. In the last 9 patients, we used the index finger of each hand for the corresponding sides. The identification of the stimulation position was determined in each case, moving the electrode from the tip of the finger until a response with maximum amplitude be reached, using the ischial tuberosity as reference. Stimulation for a duration of 0.2 milliseconds (ms) was performed, and the intensity was increased until reaching the supramaximal response (above which intensity variations do not promote amplitude alterations in the bulbocavernosus muscle). Answers were registered using filters of between 20 Hertz (Hz) and 10 Kilohertz (KHz) for low and high frequency, respectively. We started from an initial sensitivity of 50 microvolts per division ($\mu\text{V}/\text{div}$) and adjusted it as necessary. We used a base time of 50 ms (5 ms/div). The value of the latency was determined in the moment of starting the muscular depolarization wave deflection or wave -M began.

To compare both side latencies, the t-Student test was used for paired samples. The correlation between the latency value with the age and stature of the volunteers was calculated through Pearson's r coefficient. The same analysis was performed in relation to obstetric history (parity and number of vaginal deliveries) by using the Spearman's r coefficient. For all statistical analysis, a 5% significance level ($p = 0.05$) was adopted.

RESULTS

The exam was well tolerated by the volunteers, who did not report any alterations or discomfort that persisted after its conduction. Registrations of both sides presented the M-wave of the same sig-

nal when obtained with the same hand, and inverse signals when each side was approached by fingers from opposite hands (Figure-2). In performing the exam, the M-wave was obtained in all 14 cases on the right side and in 8 (57.1%) on the left side when the same hands were used for both sides. In the last 9 patients, the M-wave was obtained in all volunteers on the right side and in 5 (55.6%) on the left side when fingers of each hand were used for the corresponding sides.

Mean latency time obtained on the right and left sides was, respectively, 1.99 ± 0.41 (1.00 - 2.40) and 1.92 ± 0.48 (1.00 - 2.60) milliseconds (ms). There was no difference between latency values obtained on both sides ($p = 0.66$). There was no correlation of the motor latency of each side with age, stature and obstetric history (Table-2).

The average of the latencies obtained was compared to the values described in the literature for the transrectal approach. The results are showed as floating bars, and the distance between the lateral extremities represents the values of the arithmetic mean of each study added and subtracted from 2 corresponding standard errors. The findings of the present study are in agreement with previously published data (Figure-3).

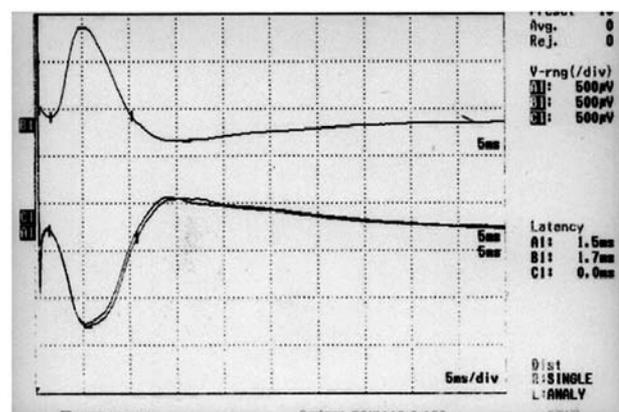


Figure 2 – Registrations of the M-wave. Superior and inferior traces were obtained, respectively on the right and left. They present inverted signals due to the opposed functions performed by the bipolar registration electrodes (active and reference) when we utilize each hand on its corresponding side.

Table 2 – Correlation between the latency value on each side, the general characteristics, such as age (years), stature (cm), parity (number of deliveries) and the number of vaginal deliveries.

	Age**		Stature**		Parity*		Vaginal Delivery*	
	r	p Value	r	p Value	r	p Value	r	p Value
Right distal motor latency	0.11	0.60	0.18	0.43	0.22	0.30	0.09	0.68
Left distal motor latency	0.26	0.37	0.06	0.85	0.17	0.58	0.07	0.81

* Spearman's r, ** Pearson's r

COMMENTS

The present study aimed to establish the applicability of the vaginal approach for the research of

pudendal nerve distal motor latency times in normal women. The results achieved were compared with those obtained in other studies through the rectal approach. As well, an analysis was made of the impact

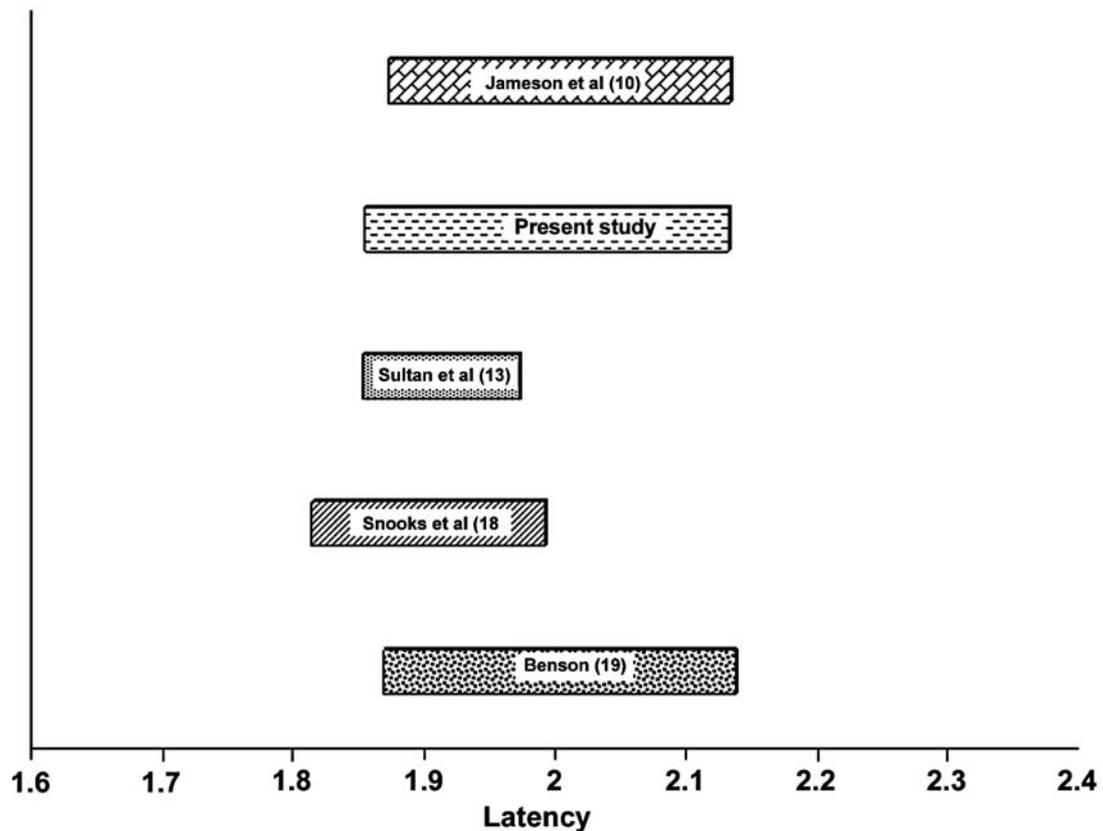


Figure 3 – Pudendal nerve distal motor latency value, corresponding to the arithmetic mean added and subtracted of 2 standard errors in the present study and in comparable literature studies. Ref. 10 = 51 women via transrectal approach; ref. 13 = 57 women via transrectal approach; ref. 18 = 20 women via transrectal approach; ref 19 = 20 women via transrectal approach.

of physiological factors, such as age, stature and parity. Despite potential advantages in some aspects utilizing needle EMG, this comparison was not our objective. The St. Mark's electrode was incorporated for clinical studies due to the facility and trustworthiness of its results and its intravaginal use aims at making it even more practical and tolerable.

The sample size of 23 patients in our study corresponded to the values of the studies utilized for comparison of viability found in the literature. They describe a universal difficulty in obtaining normal volunteers for studies of this nature, which is a probable reason for the lack of assessments in larger populations. The definition of the sample through well defined inclusion and exclusion criteria allowed the determination of values of this electrophysiological exam in a group consisting of women of different ages and obstetric histories, even though presenting no urogenital alterations.

We could not find differences regarding age and corporeal stature in pudendal motor conduction. There is no consensus in the literature regarding the interference of these factors. Jameson et al. (10) have described an extension of pudendal nerve distal motor latency that comes with aging – both in men and women without anorectal alterations. The same behavior in men suggest that other variables such as menopause, potentially related with age, did not interfere in the value of latency in women (11). Similar results were also observed when groups of men and women below 50 years of age were compared (12). However, other researchers did not confirm the influence of age and stature in motor latency using the transrectal approach (13, 14). The present work corroborates the absence of such differences, demonstrating that there are no electrophysiological alterations with aging and stature. There is no description in the literature of transvaginal studies similar to this.

Consequences of vaginal delivery and parity in the neurological integrity of the pelvic floor have been a reason for interest and studies. Alterations in pudendal motor latency could already be observed after delivery both in primiparous and multiparous women (13). It is probable that vaginal delivery occurrences can cause transitory neurogenic alterations in the pelvic musculature. However, since vaginal

deliveries have not occurred recently, immediate repercussions were not found. According to Wall (15), other associated factors such as the use of forceps, extended expulsive periods during labor, significant perineal ruptures and fetal macrosomia seem to be necessary so that the compromise of pudendal innervations is permanent with definitive abnormalities in neurophysiologic tests and clinical repercussion in the inferior and genital urinary tract.

The utilization of the St. Mark's pudendal electrode for stimulation and registration of pudendal nerve distal motor latency has shown to be effective in obtaining a clean and distinctive answer, which favors standardizing the method. Since it is a study of conduction speed, it assesses only the faster conduction nervous fibers, and thus it is not a good indicator for muscular denervation (16). The amplitude of the answer theoretically reflects the number of excitable motor units and would be a more adequate parameter than latency to identify peripheral neurological lesions. However, its variability with technical and biological factors makes its practical use difficult (10). We should also bear in mind that even though there is a delay in nervous conduction, it is improbable that a pathological effect that would affect the nerve would be sufficient to instigate an increase in the latency value in 1 ms, and that this would be able to influence the time of the reflex answer of motor units (3).

However, contrary to what occurs in pathologies of members, generally when the main nerve trunk is involved neurogenic lesions in the pelvic floor are preferably localized in the distal portion next to the muscle (16). This aspect permits that, despite the limitations of motor conduction conventional studies, pudendal nerve distal motor latency time can detect abnormalities in perineal terminal innervations.

The majority of the authors have approached the pudendal nerve transrectally. The anal sphincter represents a muscular structure suitable as a registration site due both to its external and distal to stimulation, as well as the sufficient quantity of muscle fibers for obtaining an adequate response. Differently from the classic approach, the present study used the transvaginal approach for stimulation and registration, since this approach offers better acceptance and

comfort for the woman, who is familiar to periodic gynecological exams. Stimulation and registration could be performed in an efficient way on the right side (using the right hand of a right-handed researcher). However, registration on the left side was not obtained consistently in a significant number of cases (43.5%), as well as the need for a higher intensity of stimulation to obtain a supramaximal registration. The obtainment of a response on the left side was insufficient, both with the efforts on both sides with the same hand and with corresponding hands. Difficulties in positioning the registration electrodes in contact with the bulbocavernosus muscle during the research conducted on the left side seems to be the most probable cause of the differences in findings. This means that in left-handed observers the tendency could be reversed. According to Lefaucheur et al. (12), artifacts and signal distortions could occur with the introduction of the finger and attempt to adequately locate the stimulation point. The research of the pudendal motor latency time with the index fingers of both hands caused different signal registrations due to the opposing function performed by bipolar registration electrodes (active and reference).

The latency value did not present any difference between both sides. This was a different result from other researchers that have identified a tendency in obtaining more prolonged left pudendal latency (12). The bilateral approach, even though recommended for the identification of unilateral neuropathies with possible clinical relevance (17), is limited in this method due to the irregularity in obtaining registration on both sides in normal volunteers.

The findings in the present study agree with the results reported in the literature concerning the latencies obtained through the transrectal approach in normal women (10,13,18,19). This suggests that, in clinical practice, the values obtained can be interpreted independently from the approach used and represent pudendal nerve distal motor conduction since the anal sphincter and the bulbocavernosus muscle are supplied by fibers of similar diameter and the distance between the site of stimulation and registration do not change – a fact that is confirmed by the observations of Tetzschner et al. (8). For the same reason, the results shall present variations in relation to gender.

This examination can represent a favorable beginning of a more encompassing study to verify the neurological integrity of the pelvic floor involving other electrophysiological methods, such as motor conduction studies, function and sensitive conduction (research of electric limits and evoked potentials) and research of sacral reflexes (20), making the investigation broader and more precise.

This study allowed familiarization with the neurophysiologic technique described, and correlates the results with some important variables. Our findings in volunteers without urinary symptoms add up to the few number of cases existing on normal values in asymptomatic people, allowing future comparison with patients that present voiding dysfunctions.

CONCLUSIONS

The vaginal approach has proved to be an alternative to the classical transrectal approach for the evaluation of pudendal nerve distal motor latency time, by using the St. Mark's electrode. Aging, stature and parity did not interfere in the latency value. The values of normality obtained herein for this method might serve as a comparative basis for subsequent physiopathological studies.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Pudendal nerve distal motor latency time registration appeared as a promising alternative in the neurofunctional assessment of the pelvic floor, since the measurement of the speed of nervous motor conduction is not applicable in this region. The development of the St. Mark's electrode has made the application of this neurophysiological test easier.

In most centers, the research of pudendal distal motor latency time is made through the transrectal approach. In the present study, the authors prospectively assess the use of the vaginal approach for this neurophysical registration in normal women. It is worth mentioning the difficulty of conducting a study in normal patients. Yet despite the justifications presented by the researchers regarding the discomfort reported by the patients when undergoing the transrectal approach, both approaches (vaginal and rectal) have not been compared in the same patient, revealing a point of uncertainty about the method and, as a result, in analysis of the results. This demonstrates the importance of demonstrating the viability of executing pudendal nerve distal motor latency research through the vaginal approach, as well as its normal reference values.

There are a considerable number of publications establishing pudendal distal motor latency val-

ues in patients with stress urinary incontinence, pelvic prolapse and its variations by age, biotype and previous surgeries (1,2). However, there is still no consensus regarding the validity of this assessment value since there is a great variation in its specificity, sensibility and reproducibility. An example of this is the decision of the American Gastroenterological Association recommending the use of the pudendal distal motor latency registration in the assessment of people with fecal incontinence (3). Its practical application in female urology and other voiding dysfunctions lacks complementary studies.

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Technique of Kidney Transplantation in Mice with Anti-Reflux Urinary Reconstruction

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ABSTRACT

Experimental models of organ transplantation play a crucial role in establishing the principles of transplantation immunobiology. Murine transplant models of vascularized organs are particularly useful for immunobiological studies because there are more immunological tools available. However, the technique of kidney transplant in mice is very challenging. A difficult aspect of this model is urinary reconstruction, which is frequently associated to complications. In this article, the technique of mouse kidney transplantation using an anti-reflux system (modified extravesical ureteroneocystostomy) is described and illustrated for the first time. Although technically demanding, this procedure is feasible and may reduce the incidence of urine leakage and reflux.

Key words: kidney transplantation; experimental model; mouse; microsurgery
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INTRODUCTION

Transplant models of vascularized organs in the mouse are particularly useful for immunobiological studies because there are more immunological tools available (inbred, transgenic and knockout animals; genetic mapping, monoclonal antibodies, reagents, etc.) (1,2).

The technique of mouse kidney transplantation was first established by Skoskiewicz & Russel already in 1973 (3), then improved by Kalina (4) and Zhang (5). However, it is currently performed only in a few transplantation centers in the world, due to the anastomoses complexity (renal artery diameter 0.3 mm).

SURGICAL TECHNIQUE

Male inbred C57BL/6 mice (Jackson Laboratories) weighting 20-30 g were used for kidney transplantations. Animals were housed and cared for in accordance with our institution's guidelines for experimental animals. In a small series of 20 animals, consecutively operated using this technique, the failure rate was 50% and apparently related to vascular complications.

Mice were anesthetized with a solution of ketamine (80 mg/kg i.p.) and xylazine (5 mg/kg i.p.) mixed in a normal saline solution. All procedures were performed at 4-25x magnification using a microscope (SMZ800, Nikon, Japan) and standard microsurgical instruments.

Donor Operation

After induction of anesthesia, the mouse was shaved, fixed on the operating board and the abdomen was prepped with betadine. To assure normal volemia, a saline solution was instilled in the abdominal cavity whenever it became dry. A midline incision from the xyphoid appendix to pubis was performed and exposure was achieved using small retractors to keep liver and bowels away from the left kidney.

The renal vein and artery were dissected apart under X20 magnification avoiding direct manipulation of the vessels. Left adrenal and testicular vessels were ligated with 10-0 polypropylene sutures and divided. Then, the kidney was separated from the perinephric fat and adrenal gland, the ureter was dissected freely down to the bladder without stripping its fat and cut with a small (1-2 mm) bladder patch. After clamping the aorta above the renal artery, a 30-gauge needle was introduced into the aorta, the inferior (caudal) vena cava was cut and the graft perfused with 1.0 mL cold heparinized saline solution (100U/mL). Renal vessels were cut with a Carrel patch of the aorta and vena cava and the graft was removed and stored in a normal saline solution at 4°C for 20 min. until the time of transplantation (Figure-1).

Recipient Operation

To increase the success rate, a two-stage procedure was performed, i.e. the left native kidney was removed at the time of grafting and the right native kidney was left in place until day 7, when the right nephrectomy was performed.

A midline incision from the xyphoid appendix to pubis was performed, and exposure was achieved using small retractors to keep liver and bowels away from the kidney. The renal pedicle was ligated with 7-0 silk suture and the recipient left kidney was removed leaving place for the donor kidney.

After ligating some lumbar branches, the infrarenal aorta and inferior vena cava were isolated and two loops of 7-0 silk were placed proximally and distally around them and tied to promote homeostasis. Elliptical longitudinal aortotomy and cavotomy were performed between these ties and the vessels were flushed to clear blood inside them. Vascular

anastomoses were performed end-to-side to the abdominal aorta and vena cava using a running 11-0 nylon suture (Ethilon, Ethicon, USA). To anastomose the renal artery, two stay sutures (11-0 nylon suture) were placed at the artery's opposite ends (inferiorly and superiorly). The back wall was sewn first, through a transluminal approach; then the anterior wall, both with a continuous suture. In general, only four to five stitches on each side are necessary to avoid bleeding.

The vein was anastomosed in the same fashion as the artery. Before suturing the vein, it is important to confirm it is not twisted. Depending on the size of the caval patch, 5 to 7 times the vein was stitched on each side, avoiding pinching the opposite wall. After both anastomoses were performed, the first distal loop was loosened and then the proximal loop. Blood flowed back into the kidney and bleeding was minimal. Saline was usually given subcutaneously proportional to the bleeding (Figure-2).

Urinary reconstruction was established by suturing the small bladder patch to a cystotomy located on the bladder dome (similar to the Lich-Gregoir technique for extravesical ureteroneocystostomy). The animal should be well hydrated to keep the bladder filled. First, the serosa and muscular layers of the posterolateral aspect of the bladder were divided (5 mm) with the micro-scissors avoiding major vessels and taking care not to enter the bladder. This develops a plane between the muscularis and mucosa allowing the mucosa to bulge out. Then, the bladder mucosa was divided (2 mm) and sutured to the mucosa of the patch from the donor's bladder with a running 11-0 nylon suture (Ethilon, Ethicon, USA). Then, one interrupted seromuscular suture was placed in each quadrant of the patch, and finally three interrupted 11-0 nylon seromuscular sutures were loosely placed over the patch to close the bladder muscle over the bladder patch and terminal ureter, burying the anastomosis, sealing the first suture and creating a muscular tunnel to reduce the risk of urine reflux (Figure-3).

Abdominal wall and skin were closed with a continuous 5-0 absorbable suture (Vycryl, Ethicon, USA). A saline 0.5 mL solution was given subcutaneously after the transplant and no antibiotics

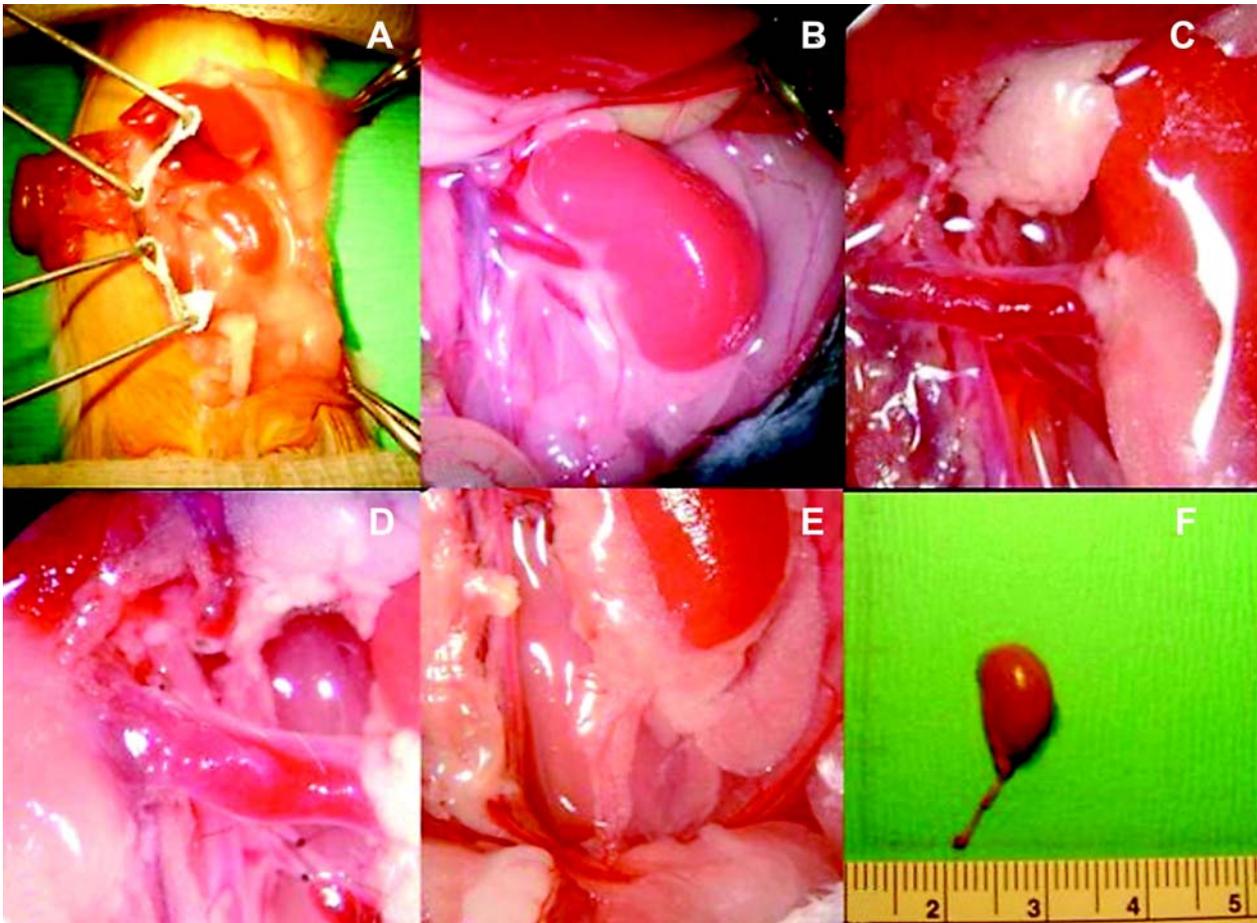


Figure 1 – Donor operation. A and B) Left kidney before dissection (B, X4). C) The renal vein and artery were dissected apart (X8). D) Left adrenal and testicular vessels were ligated and divided (X10). E) The kidney was separated from perinephric fat and adrenal gland, the ureter was dissected freely down to the bladder. After clamping the aorta above the renal artery, a 30-gauge needle was introduced into the aorta, the inferior vena cava was cut and the graft perfused with 1.0 ml cold heparinized saline solution (100U/mL), X4. F) Renal graft shown in relation to a millimetric scale. The renal vessels were cut with a Carrel patch of the aorta and vena cava (not shown) and the ureter removed together with a small (1-2 mm) bladder patch. Then, the graft was removed and stored in a normal saline solution at 4°C while the recipient was prepared (X2).

or heparin were given. Mice were kept under a heating lamp until they were awake.

COMMENTS

Mouse kidney transplantation is a very demanding microsurgical procedure full of details, which requires long training and meticulous technique. The murine kidney is extremely sensitive

to ischemia/reperfusion injury, and to perform a successful operation the time of anastomosis (warm ischemia) should be less than 35 minutes. Most experiments show that in experienced hands the survival rate is between 40 and 70% (3,4). The learning curve is slow because the risk of renal artery thrombosis is very high and difficult to avoid, and due to urological complications.

In rat kidney transplantation, continuity of urine flow is reestablished most commonly by end-

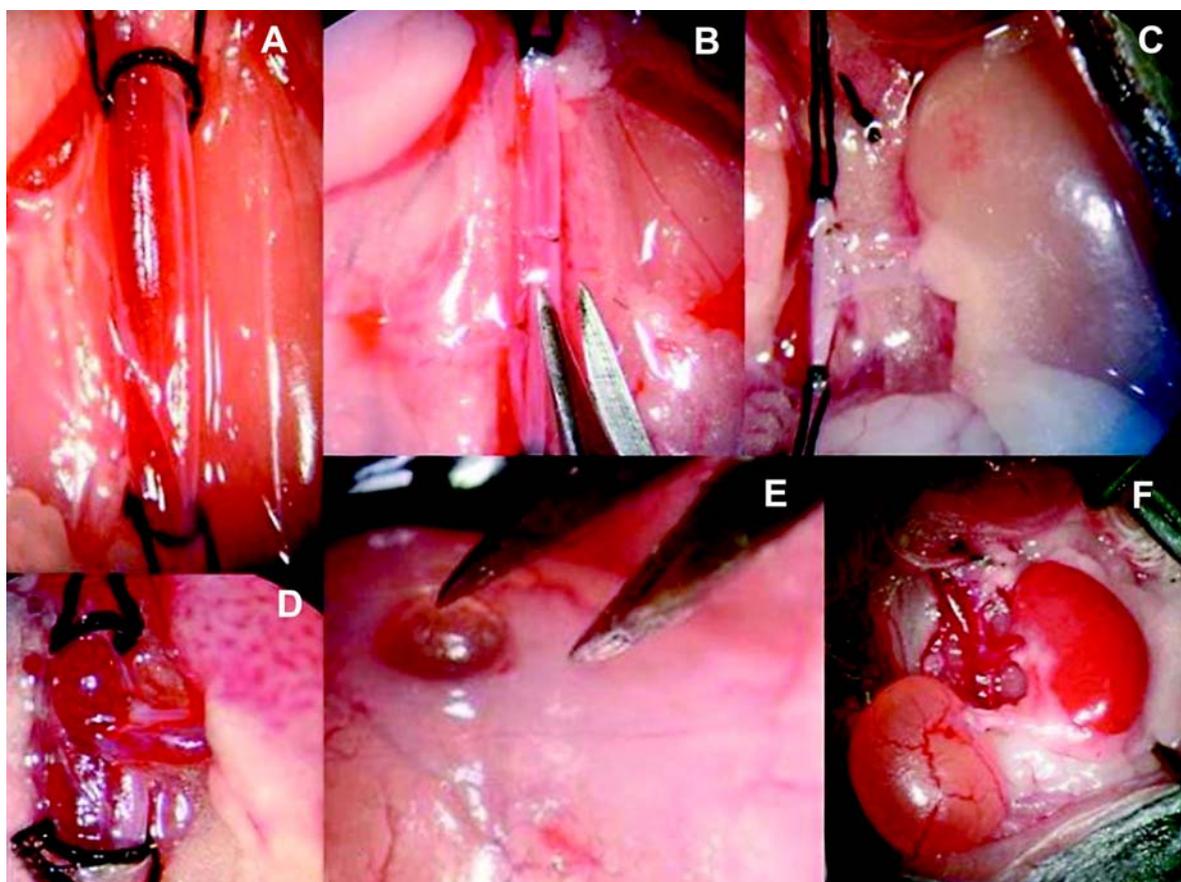
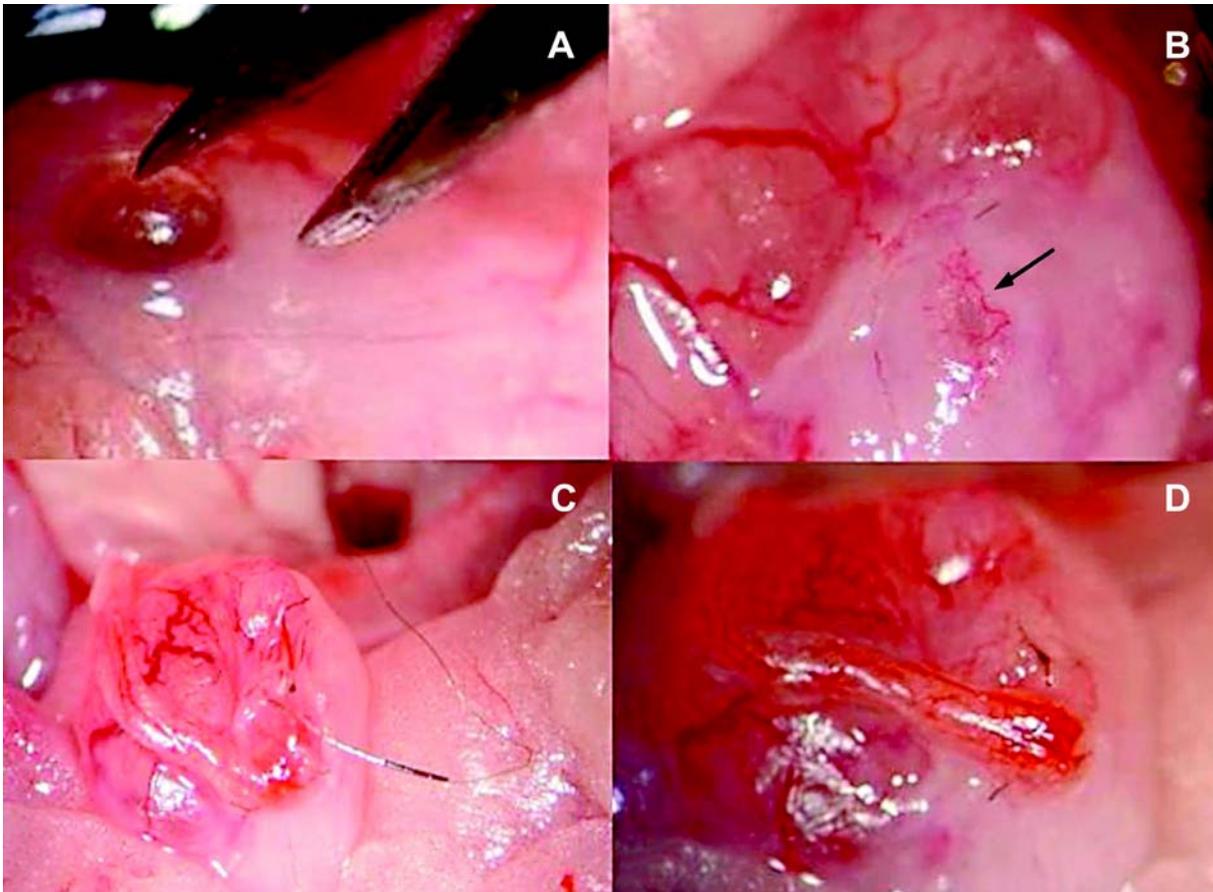


Figure 2 – Technique of mouse kidney transplantation. A) The infrarenal aorta and inferior vena cava were isolated and 2 loops of 7-0 silk were placed proximally and distally around them and tied (X12). B) Elliptical longitudinal aortotomy and cavotomy were performed (X10). C) Vascular anastomoses were performed end-to-side to the abdominal aorta and vena cava (X8). D) After both anastomoses were concluded, the loops were loosened and the graft reperused (X8). E) Urinary reconstruction was established by suturing the bladder patch to a cystotomy located on the bladder dome (X12). F) Kidney graft after anastomosis (X2).

to-end ureter-ureter anastomosis (splinted or non-splinted). On the other hand, kidney transplantation in mice, probably because of the very small diameter of the ureter, ureter-to-ureter anastomosis has not been described. In the literature, urinary reconstruction in mouse kidney transplantation has been performed either by direct implantation of the ureter in the bladder without anastomosis or most commonly by bladder-to-bladder anastomosis using a large bladder patch. The blood supply of the terminal ureter and bladder patch is exclusive from the graft vasculature and prone to ischemia. Not uncommon, the use of a

large bladder patch is associated with either bladder necrosis and urine leakage or neurogenic bladder with calculi formation due to bladder denervation (6).

The most preferred technique for urinary reconstruction in clinical kidney transplantation is extravesical ureteroneocystostomy. Differently from the technique of extravesical ureteroneocystostomy used in the clinic, the author opted for using a small bladder patch since spatulation of the mouse ureter would be difficult. No splint was used since it has been associated with more urological complications (6), and the bladder patch allows enough area to



Figures 3 – Urinary reconstruction using a bladder-to-bladder anastomosis and an anti-reflux technique similar to an extravesical ureteroneocystostomy. A) The serosa and muscular layers of the bladder were divided (4 mm) forcing the mucosa to bulge outward (X16). B) and C) A 2 mm incision was performed in the bladder mucosa (arrow) and sutured to the mucosa of the patch from the donor's bladder with a running 11-0 nylon suture (X10 and X8, respectively). D) One interrupted seromuscular suture was placed in each quadrant of the patch, and finally 3 seromuscular stitches were loosely placed to close the bladder muscle over the bladder patch (X10).

place sutures. The technique described here avoids continuous (running) suture of muscular layer that increases ischemia and the risk of patch necrosis and urine leakage. Water-tightness is ensured by minimal vesical opening and continuous suture. The incidence of vesical calculi depends also on the suture material used for urinary reconstruction (6), and therefore, newer absorbable microsutures are preferred.

An anti-reflux system, although time-consuming and difficult to perform, may reduce the incidence of urosepsis related to urinary fistulae and reduce the risks of hydronephrosis and chronic pyelonephritis in the long-term. To the author's

knowledge this is the first report on urinary reconstruction in the mouse using an anti-reflux technique. The potential advantages of this technique applied in the murine model still need to be confirmed in the long-term in case-control studies.

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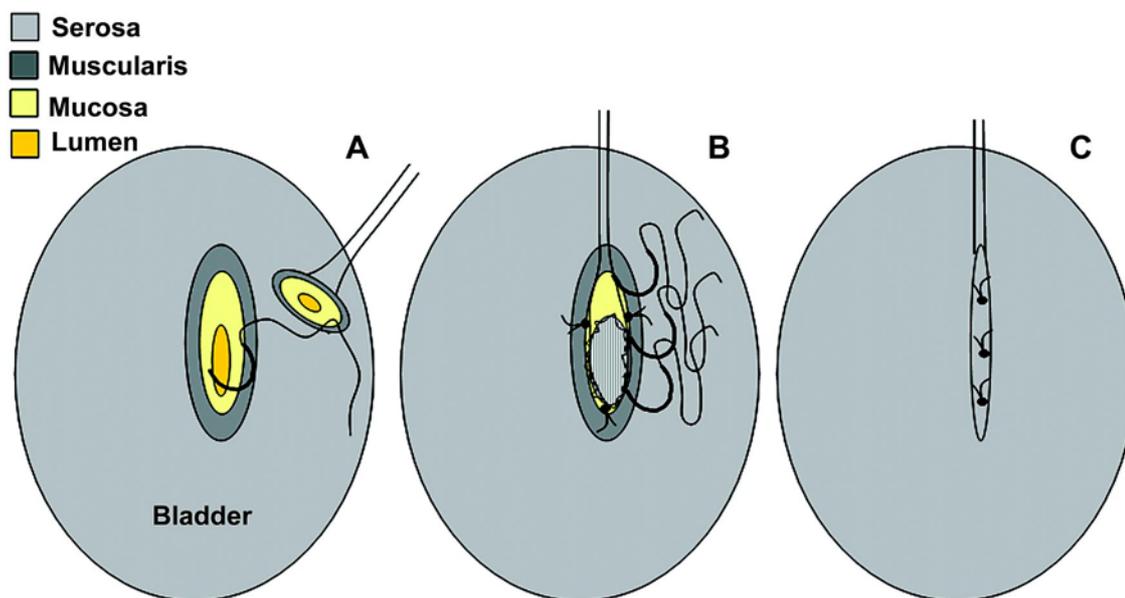


Figure 4 – Schematic drawings of the ureterovesical anastomosis steps, as shown in Figure-3.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Clinical kidney transplantation has become the preferred method of renal replacement therapy worldwide. Testing new pharmacological and biological agents, and identifying new methods to diagnose and treat rejection depends on preclinical investigation. The use of large animal models such as the monkey, dog, cat, pig, etc. in transplant research has become problematic due to high cost, the need for specialized animal care, longer gestation and life spans, and cultural sensitivities regarding certain species. Therefore, the rodent is usually preferred. The rat is of sufficient size (300-400 grams) to permit solid organ transplant experiments using microsurgical techniques, but has been less well characterized than the mouse in molecular biology. Since much of the focus on molecular immunology and genetics has been targeted to murine models (monoclonal antibody production, transgenics, knock in and knock out recombinations,

etc.), the mouse is better suited to transplant experimentation. However, the adult mouse (30-50 grams) is 5-10 times smaller than the rat, more difficult to perform microsurgery, and ultimately more prone to technical failures. A major limiting factor in murine whole organ kidney transplantation has been the ureteral reconstruction. The author offers a nice technique of simplifying the anastomosis of the small ureter by using a donor bladder patch. This technique, similar to the human extravesical ureteral anastomosis, may also limit post transplant urinary infections by creating an anti-reflux tunnel. Any approach that simplifies microsurgical transplant techniques in murine models would be a welcome addition to this difficult endeavor. This technique should be tried by other murine microsurgical teams to see if diminished technical failures can reinvigorate the wider use of murine kidney transplants for long term models.

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EDITORIAL COMMENT

The author reports for the first time a modified extravesical ureterocystoneostomy for urinary tract reconstruction in the mouse kidney transplant model. After completion of the vascular anastomosis the bladder dome is incised over a length of 5 mm avoiding cutting into the mucosa. The mucosa is opened at the distal end of the submucosal tunnel over a distance of approximately 2 mm. The transplant ureter together with its distal end and a small bladder patch is then anastomosed to the mucosa. Thereafter, the muscularis of the bladder wall is readapted over

the implanted transplant ureter with 3 interrupted sutures.

Since the first description by Fisher & Lee, the use of rat-inbred strains as an investigational model of renal transplantation has been extensively used (1). Microsurgical techniques have been developed to the extent that the postoperative survival of renal grafted rats is now routine. However, renal transplantation in mice is technically very demanding due to the small vessels size and the inherent risk of vascular thrombosis and graft loss. Furthermore,

reconstruction of the urinary tract has been associated with upper urinary tract obstruction as well as ureter and bladder patch necrosis (2). The learning curve in kidney transplantation in mice is substantially longer than in rats and the mortality rate, as stated by the author, is as high as 50%, even in the hands of experienced microsurgeons and long-term survival rates are sparse. A survival rate of more than 4 weeks has been reported by the same author in only 4 animals (8%) in a consecutive series of 50 kidney transplant procedures in mice using a bladder to bladder patch for urinary tract reconstruction (3). Most animals died due to surgical related complications.

Therefore, it seems of utmost importance to balance the advantages and disadvantages of performing a technical demanding antireflux procedure during kidney transplantation in mice. Prolonged surgical time in small animals, as for performing an extravesical ureterocystoneostomy, may lead to hypothermia and eventually death and has to be considered as a major risk factor (4). Further, performing an antireflux procedure does not inevitably allow drawing the conclusion that there is no vesicoureteral reflux and that the graft is protected

against the possibility of upper urinary tract infection. In humans the key to success to prevent vesicoureteral reflux according to Grégoir is to create a submucosal tunnel of 5 to 6 cm length (5). However, it remains to be determined how long the submucosal tunnel has to be in mice to prevent vesicoureteral reflux.

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STONE DISEASE

Forced Versus Minimal Intravenous Hydration in the Management of Acute Renal Colic: A Randomized Trial

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J Endourol. 2006; 20: 713-6

Background and Purpose: The management of acute renal colic is a problem commonly encountered by both urologists and emergency medicine physicians. The classic approach to managing uncomplicated acute renal colic involves hydration, along with imaging and pain control. Previous studies have suggested that hydration has a significant impact on patient comfort, as well as spontaneous stone passage. This study evaluated the effects of maintenance vs forced hydration and its effect on the pain experienced from renal colic.

Patients and Methods: Forty male and 18 female patients with a mean age of 41 years suspected to have acute renal colic were identified in the emergency department. After screening and informed consent, the patients were enrolled in the study, and 43 patients were eventually available for analysis. Patients received intravenous (IV) analgesia, imaging with a noncontrast CT scan of abdomen and pelvis, and assignment to either forced IV hydration with 2 L of normal saline over 2 hours (N = 20) or minimal IV hydration at 20 mL of normal saline per hour (N = 23). A visual analog pain scale was completed hourly for a total of 4 hours. Demographic information, laboratory and imaging results, narcotic use in morphine equivalents (ME), and pain scores were recorded and compared. Spontaneous stone passage rates were also calculated by careful patient follow-up. Results were considered statistically significant at $p < 0.05$.

Results: Stone size was equivalent in the two treatment groups ($p > 0.05$). There was no difference in the narcotic requirement in ME ($p = 0.644$) between the two groups. Similarly, there was no difference in hourly pain score or stone-passage rates between the groups ($p > 0.05$).

Conclusions: Treatment of uncomplicated renal colic has traditionally included vigorous intravenous hydration, as well as medications for the control of pain and nausea. Our data suggest that maintenance intravenous fluids are as efficacious as forced hydration with regard to patient pain perception and narcotic use. Moreover, it appears the state of hydration has little impact on stone passage.

Editorial Comment

This study demonstrates that in the emergency room (ER) setting, forced hydration for acute renal colic does not impact pain or stone passage. However, it is important to note that this study evaluates hydration only in the acute ER setting. It is common practice for patients to be instructed to force oral hydration after discharge from the emergency room. Compliance with this recommendation and its impact on subsequent stone passage was not evaluated in this study, and may be worthwhile of further investigation. While the study relies on chart review and self-reporting to document stone passage, other studies have suggested that self-reporting of stone passage may be inaccurate in a significant proportion of patients. The authors do not report the duration of follow-up or time to stone passage, though the 30% spontaneous stone passage rate is lower than one might expect in relation to the mean stone size. Location of ureteral calculi was not reported, and could be a confounding variable in the equation. In addition, the utility of forced hydration may depend on the fluid status of the patient and the time from onset of pain to presentation to the ER. As renal hemodynamics adapt to obstruction within the first 24 hours, the impact of hydration may diminish with delayed presentation. It may be useful to evaluate

response to hydration based on the presence of volume depletion (BUN/CR ratio) and the time to presentation (< or > 24 hours from onset of pain).

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One Week of Ciprofloxacin Before Percutaneous Nephrolithotomy Significantly Reduces Upper Tract Infection and Urosepsis: A Prospective Controlled Study

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BJU Int. 2006; 98: 1075-9

Objective: To evaluate whether 1 week of ciprofloxacin before percutaneous nephrolithotomy (PCNL) in patients with stones of > or = 20 mm or pelvicalyceal dilatation, reduces urosepsis, as we previously reported that such patients have four times the risk of urosepsis after PCNL.

Patients and Methods: Patients undergoing PCNL, and who fulfilled strict selection criteria, were recruited prospectively into a study which was conducted in two phases. The study methods were similar to those previously described; patients with dilated pelvicalyceal systems and/or stones of > or = 20 mm from phase 1 (previously published) acted as controls. In the subsequent phase, the same selection criteria applied and only those with stones of > or = 20 mm and/or dilated pelvicalyceal systems were given ciprofloxacin 250 mg twice daily for 1 week before PCNL and comprised the treatment arm. Midstream urine samples, renal pelvic urine and fragmented stones were collected to assess culture and sensitivity. Systemic inflammatory response syndrome (SIRS) was used to define urosepsis after PCNL. The urologists monitoring the patients after PCNL and conducting the analysis were all unaware of the characteristics of the stones or intravenous urography findings before PCNL. In all, 115 patients (54 in phase 1 and 61 in phase 2) were recruited, of whom 46 in phase 1 and 52 in phase 2 had stones of > or = 20 mm and/or a dilated pelvicalyceal system, and became the control and treatment arms, respectively.

Results: The patient demographics were similar in both arms. There was three times less risk of upper tract infection (relative risk 3.4, 95% confidence interval 1.0-11.8, P = 0.04) and SIRS (2.9, 1.3-6.3, P = 0.004) in the patients receiving ciprofloxacin (treatment arm).

Conclusions: The administration of oral ciprofloxacin for 1 week before PCNL in patients with stones of > or = 20 mm or dilated pelvicalyceal systems significantly reduced the risk of urosepsis.

Editorial Comment

The authors selected patients with significant hydronephrosis or stone burdens greater than 2 cm as candidates for this study, based on an initial study, which suggested that these patients were at greater risk for having an infected upper tract at the time of PCNL (1). However, this study also concluded that there was no correlation between SIRS and stone burden or degree of hydronephrosis.

This is a non-blinded non-randomized study comparing results to a historical cohort. Accepting these limitations in study design, the results are still dramatic with regards to the 3-fold decrease in upper tract infection and SIRS. I am still not convinced regarding the clinical relevance of SIRS as defined by the criteria presented. For example, pain may increase the HR and RR, which would satisfy the criteria for SIRS. The stress of surgery can cause transient leukocytosis. Elevations in temperature and respiratory rates may be related to

atelectasis. Preoperative antibiotics would not be anticipated to impact any of these events. The authors do not state what measures were taken to exclude other common causes of fever, tachycardia, and tachypnea during post-PCNL recuperation, such as atelectasis, hypovolemia, and pain. The Consensus panel that developed the definition of SIRS states that it is “overly sensitive and non-specific”, and caution that major surgical procedures as well as cardiogenic events may result in the clinical picture similar to SIRS(2). The consensus panel also cautions that sepsis should be defined as the presence of SIRS and infection.

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ENDOUROLOGY & LAPAROSCOPY

Laparoscopic Dismembered Pyeloplasty in Children Younger Than 2 Years

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J Urol. 2007; 177: 335-8

Purpose: Since the first laparoscopic pyeloplasty was described in a child in 1995, there have been several reports of pyeloplasty in older children. However, to date there have been few reports of laparoscopic pyeloplasty in infants and toddlers. The aim of this study was to evaluate the results of laparoscopic pyeloplasty in children younger than 2 years.

Materials and Methods: All laparoscopic Anderson-Hynes pyeloplasties performed in children younger than 2 years were retrospectively reviewed. The diagnosis of ureteropelvic junction obstruction was confirmed on renal sonography and diuretic renogram. Laparoscopic pyeloplasties were performed via a transperitoneal route as originally described, with key modifications. All children were investigated with postoperative diuretic renogram and renal ultrasonography.

Results: A total of 38 children with ureteropelvic junction obstruction underwent laparoscopic Anderson-Hynes Pyeloplasty between January 2001 and December 2005. Of these patients 11 (7 males and 4 females) were younger than 2 years at surgery (median 1.4, range 2 to 22 months) and 1 had bilateral ureteropelvic junction obstruction, for a total of 12 primary repairs. However, 2 patients (17%) required redo laparoscopic pyeloplasty, for a total of 14 laparoscopic dismembered pyeloplasties in this age group. Operative time ranged from 70 to

140 minutes (mean 100) and median hospital stay was 2 days. Followup studies showed normal drainage in all patients except 1, who after redo pyeloplasty exhibited significantly improved but still prolonged drainage.

Conclusions: This study suggests that laparoscopic pyeloplasty can now be performed in young children with good results.

Editorial Comment

Laparoscopic Pyeloplasty still remains controversial in the pediatric population. The new era of reconstructive surgery with better laparoscopic knowledge and instrumentation, i.e.; fine needlescopic (minilaparoscopic) instruments, facilitated the ease of executing a precise and delicate reconstructive surgery, allowing surgeons to perform the anastomosis without handling or traumatizing the ureter or pelvic mucosa.

In a retrospective study, the authors evaluated their experience of 14 laparoscopic dismembered pyeloplasties performed in patients less than 2 years-old. The data demonstrated feasibility of this surgical technique with a good outcome measured objectively by nuclear renal lasix scan but with no subjective evaluation (pain free postoperatively).

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Laparoscopic Ice Slurry Coolant for Renal Hypothermia

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J Urol. 2007; 177: 382-5

Purpose: We assessed the safety and efficacy of microparticulate ice slurry for laparoscopic hypothermia during renal ischemia in a single kidney porcine model.

Materials and Methods: A total of 18 farm pigs were randomized to 3 groups of 6 each. All groups underwent initial right laparoscopic nephrectomy, followed by 1 of 3 procedures on the left kidney. Group 1 underwent 90 minutes hilar clamping under warm ischemia, group 2 underwent 90 minutes hilar clamping under cold ischemia using laparoscopically delivered microparticulate ice slurry and control group 3 underwent hilar dissection, no clamping and no microparticulate ice slurry. Body and renal cortical temperatures were measured. Serum creatinine and the glomerular filtration rate were assessed preoperatively, and on postoperative days 1,3,8 and 15.

Results: Average time to achieve a renal temperature of 20°C or less was 9.7 minutes and it remained constant during the 90 minutes cold ischemia time. Mean serum creatinine was significantly higher in the warm ischemia group than in the cold ischemia and control groups on postoperative days 1 and 3. Additionally, mean serum creatinine in the cold ischemia and control groups was similar at all time points. The mean glomerular filtration rate was significantly lower in the warm ischemia group than in the cold ischemia and control groups on postoperative days 1,3 and 8. The mean glomerular filtration rate in the cold ischemia group was lower than in the control group on postoperative day 1, while it was similar on postoperative days 3,8 and 15.

Conclusions: In the porcine model laparoscopic renal hypothermia achieved with microparticulate ice slurry was safe and efficient. It significantly decreased renal dysfunction secondary to an ischemic insult with no adverse effects or complications associated with microparticulate ice slurry use.

Editorial Comment

Prevention of renal ischemia-reperfusion injury remains a challenge, particularly in laparoscopic partial nephrectomy. Gill et al. first reported the use of ice slush laparoscopically to achieve cold ischemia in laparoscopic partial nephrectomy, but the delivery system was somewhat cumbersome. Conversely, this animal study used microparticulate ice slurry (MPS) for laparoscopic hypothermia during renal ischemia in a single kidney porcine model. MPS contains smooth globular ice particles (< 100 μ m in diameter) suspended in saline carrier medium. MPS may be pumped through a 4 mm catheter without plugging, in contrast to the standard ice slush which is composed of dendritic ice crystals that do not flow through narrow tubes, making it not applicable for laparoscopic surgery but it is used for regional hypothermia during open procedures. Survival studies comparing 3 different groups (Group 1 - 90 minutes warm ischemia, group 2 - 90 minutes cold ischemia using laparoscopically delivered MPS, and control group 3 - hilar dissection, no clamping and no microparticulate ice slurry), demonstrated significant difference in renal function in group 1 when compared to other groups. The authors concluded that MPS was safe and efficient to achieve renal hypothermia and to decrease renal dysfunction due to ischemia-reperfusion injury.

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IMAGING

MRI-Guided Biopsy of the Prostate Increases Diagnostic Performance in Men with Elevated or Increasing PSA Levels After Previous Negative TRUS Biopsies

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Objectives: Repeatedly negative prostate biopsies in individuals with elevated prostate specific antigen (PSA) levels can be frustrating for both the patient and the urologist. This study was performed to investigate if magnetic resonance imaging (MRI)-guided transrectal biopsy increases diagnostic performance in individuals with elevated or increasing PSA levels after previous negative conventional transrectal ultrasound (TRUS)-guided biopsies.

Methods: 27 consecutive men with a PSA > 4 ng/ml and/or suspicious finding on digital rectal examination, suspicious MRI findings, and at least one prior negative prostate biopsy were included. Median age was 66 years (mean, 64.5 +/- 6.8); median PSA was 10.2 ng/ml (mean, 11.3 +/- 5.5). MRI-guided biopsy was performed

with a closed unit at 1.5 Tesla, an MRI-compatible biopsy device, a needle guide, and a titanium double-shoot biopsy gun.

Results: Median prostate volume was 37.4 cm³ (mean, 48.4 \pm 31.5); median volume of tumor suspicious areas on T2w MR images was 0.83 cm³ (mean, 0.99 \pm 0.78). The mean number of obtained cores per patient was 5.22 \pm 1.45 (median, 5; range, 2-8). Prostate cancer was detected in 55.5% (15 of 27) of the men. MRI-guided biopsy could be performed without complications in all cases.

Conclusion: According to our knowledge, this is the largest cohort of consecutive men to be examined by MRI-guided transrectal biopsy of the prostate in this setting. The method is safe, can be useful to select suspicious areas in the prostate, and has the potential to improve cancer detection rate in men with previous negative TRUS-biopsies.

Editorial Comment

New biopsy strategies with increased numbers of systematically placed biopsy cores have been developed to decrease the false-negative rate associated with conventional sextant prostate biopsy; however, many men still find themselves in this clinical dilemma, and the best way to care for these patients remains uncertain. Conventional and 3D-spectroscopic endorectal magnetic resonance imaging (3D-MRSI) techniques have shown promise in the improved detection of cancer within the prostate. One important drawback of using 3D-MRSI-guided biopsy is the process of overlaying the abnormal voxel seen of spectroscopic images on transrectal ultrasound scans. In other words to project a suspicious area for cancer seen on an endorectal magnetic resonance spectroscopic imaging into the scans obtained with transrectal ultrasound in order to adequately sample the suspicious areas. The authors present in this manuscript an interesting technique of MRI-guided biopsies. They used a non-metallic, fully automatic core-needle, double shot biopsy gun and a portable biopsy device previously described. The major limitations of this study are related to the criterion used to consider suspicious lesion on conventional endorectal MR imaging of the prostate and the need for 2 consecutive MRI examinations. As we know prostate cancer of the peripheral zone appear as hypointense areas but this finding is not specific since other benign abnormalities such as inflammation, fibrosis and focal prostatic atrophy may have similar appearance. 3D-MRSI is superior to conventional MR imaging as a guide for repeat biopsy due its capacity of detect abnormal metabolic activities, thus allowing the differentiation between benign and malignant lesions. Detection of cancer in prostate with normal appearance on conventional MRI examination is also possible with 3D-MRSI. Perhaps in the near future, the ideal approach for these patients would be the use of this technique associated with 3D-MRSI of the prostate and during a single procedure.

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Dynamic Contrast Enhanced, Pelvic Phased Array Magnetic Resonance Imaging of Localized Prostate Cancer for Predicting Tumor Volume: Correlation with Radical Prostatectomy Findings

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J Urol. 2006; 176: 2432-7

Purpose: We assessed the value of pelvic phased array dynamic contrast enhanced magnetic resonance imaging for predicting the intraprostatic location and volume of clinically localized prostate cancers.

Materials and Methods: Suspicious areas on prospective pre-biopsy magnetic resonance imaging in 24 patients were assigned a magnetic resonance imaging malignancy score and located with respect to anatomical features, gland side, and transition and peripheral zone boundaries. The largest surface area and volume were measured. These magnetic resonance imaging findings were compared with radical prostatectomy specimen histopathology findings.

Results: Histopathology maps detected 56 separate cancer foci. The largest tumor focus was located in the peripheral zone in 14 patients and in the transition zone in 10. T1-weighted dynamic contrast enhanced magnetic resonance imaging identified 30 of the 39 tumor foci greater than 0.2 cc and 27 of the 30 greater than 0.5 cc. T2-weighted sequences were suspicious in 22 of 30 foci greater than 0.2 cc that were identified by T1-weighted dynamic contrast enhanced magnetic resonance imaging sequences. Sensitivity, specificity, and positive and negative predictive values for cancer detection by magnetic resonance imaging were 77%, 91%, 86% and 85% for foci greater than 0.2 cc, and 90%, 88%, 77% and 95% for foci greater than 0.5 cc, respectively. Median focus volume was 1.37 cc (range 0.338 to 6.32) for foci greater than 0.2 cc detected by magnetic resonance imaging in the peripheral zone and 0.503 cc (range 0.337 to 1.345) for those not detected by magnetic resonance imaging ($p < 0.05$). Corresponding median values for transition zone foci were 2.54 (range 0.75 to 16.87) and 0.435 (range 0.26 to 0.58).

Conclusions: Pre-biopsy pelvic phased array dynamic contrast enhanced magnetic resonance imaging is an accurate technique for detecting and quantifying intracapsular transition or peripheral zone tumor foci greater than 0.2 cc. It has promising implications for cancer detection, prognosis and treatment.

Editorial Comment

The authors present a very interesting study for the detection and prediction of prostate tumor volume using 1.5 Tesla MRI - dynamic contrast enhanced protocol with a single pelvic phased array coil. As we know, estimation of tumor volume is improved by endorectal 3D-magnetic resonance spectroscopic imaging (3D-MRSI) and endorectal dynamic contrast enhanced technique, but errors are not infrequent. Although the authors' project is based on a controversial issue (we do not agree that the pelvic phased array coil provides similar image quality in comparison with endorectal coil), their results are impressive. Endorectal MR imaging and 3D- MRSI are useful for detecting the majority of peripheral zone tumors larger than 0.5 cc (1.0 cm). So far dynamic contrast enhanced endorectal-MRI also has the capability of detecting tumor foci greater than 0.5 cc, with 85.3% sensitivity and 92.6% positive predictive value. The authors results was very impressive since they had 77% sensitivity, 91% specificity, and 86% positive and 85% negative predictive values for detecting tumor foci greater than 0.2 cc (7 mm). Another important contribution of this technique was also the possibility of detecting transition zone tumors. Further studies with larger population are necessary to confirm the value of this new imaging approach.

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UROGENITAL TRAUMA

Specific Fracture Configurations Predict Sexual and Excretory Dysfunction in Men and Women 1 Year after Pelvic Fracture

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J Urol. 2006; 176: 1540-5

Purpose: We determined the prevalence and predictors of sexual and excretory dysfunction in patients 1 year after pelvic fracture.

Materials and Methods: The multicenter Pennsylvania Trauma Outcomes Study enrolled 1,238 patients and contacted them 1 year after injury. Sexual limitations and excretory dysfunction (bladder/bowel incontinence) were defined based on responses from the Functional Capacity Index. Health related quality of life was determined using SF-36. The relationship between specific fracture patterns and dysfunction along with the effect of dysfunction on quality of life in patients with pelvic fracture were evaluated by multivariate analysis.

Results: Of 1,160 eligible patients 292 (26%) had pelvic fractures. Sexual dysfunction was reported in 21% vs 14% of those with vs without pelvic fractures and bowel or bladder incontinence was reported in 8% vs 4%. On multivariate analysis men with sacroiliac fractures were at higher risk for sexual (RR 4.0, 95% CI 2.3 to 6.8) and excretory (RR 4.3, 95% CI 1.4 to 13.5) dysfunction. In women symphyseal diastasis was associated with sexual (RR 4.8, 95% CI 2.0 to 11.2) and excretory (RR 12.5, 95% CI 1.9 to 80.2) dysfunction. Of patients with pelvic fractures men with sexual dysfunction and women with excretory dysfunction had significantly worse quality of life than those without dysfunction.

Conclusions: One year after trauma men with sacroiliac fractures and women with symphyseal diastasis were at increased risk for sexual and excretory dysfunction independent of overt pelvic organ injury. In patients with pelvic fracture male sexual dysfunction and female excretory dysfunction were associated with decreased quality of life. Our data highlight the need for further study of dysfunction following pelvic trauma and interventions to decrease the risk of long-term disability.

Editorial Comment

Erectile dysfunction after pelvic fracture is interplay of injury to the penile arterial inflow, venous outflow or nerve innervation. Clearly injuries to the pubic rami that result in bony distraction, may also displace and injury the crus of the penis. Such patients may suffer from venous leak or arterial insufficiency, or both. The arterial and nervous supply to the penis is partially protected by the fascial walls of Alcock's canal, but is vulnerable to injury if the adjacent ischial bone is fractured. Erectile dysfunction (ED) after pelvic fracture has typically been associated with concomitant urethral disruption injury. Historically, with urethral injury ED rates are up to 75%. Surprisingly, Wright et al. determined that SI fractures have the highest rates of ED. Intuitively, one would assume pubic rami and open book fractures to have high rates of male ED. Clearly, quality of life as to urinary excretory control and erectile dysfunction after pelvic fractures are issues that the urologist should be familiar with. For it is the urologic consequences of pelvic fracture that are often prolonged, morbid and difficult to manage, long after the orthopedic injuries have healed.

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Experience with Wound VAC and Delayed Primary Closure of Contaminated Soft Tissue Injuries in Iraq

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J Trauma. 2006; 61: 1207-11

Background: Wartime missile injuries are frequently high-energy wounds that devitalize and contaminate tissue, with high risk for infection and wound complications. Debridement, irrigation, and closure by secondary intention are fundamental principles for the management of these injuries. However, closure by secondary intention was impractical in Iraqi patients. Therefore, wounds were closed definitively before discharge in all Iraqi patients treated for such injuries at our hospital. A novel wound management protocol was developed to facilitate this practice, and patient outcomes were tracked. This article describes that protocol and discusses the outcomes in a series of 88 wounds managed with it.

Methods: High-energy injuries were treated with rapid aggressive debridement and pulsatile lavage, then covered with negative pressure (vacuum-assisted closure [VAC]) dressings. Patients underwent serial operative irrigation and debridement until wounds appeared clean to gross inspection, at which time they were closed primarily. Patient treatment and outcome data were recorded in a prospectively updated database.

Results: Treatment and outcomes data from September 2004 through May 2005 were analyzed retrospectively. There were 88 high-energy soft tissue wounds identified in 77 patients. Surprisingly, for this cohort of patients the wound infection rate was 0% and the overall wound complication rate was 0%.

Conclusion: This series of 88 cases is the first report of the use of a negative pressure dressing (wound VAC) as part of the definitive management of high-energy soft tissue wounds in a deployed wartime environment. Our experience with these patients suggests that conventional wound management doctrine may be improved with the wound VAC, resulting in earlier more reliable primary closure of wartime injuries.

Editorial Comment

The vacuum assisted closure system is an effective, simple, and under-utilized method to help repair and close wounds. In the Iraq War, many of the injuries have devastating soft tissue defects that are ideal for negative pressure wound therapy. Numerous urologic injuries have also been seen during the Iraq conflict. Such complex urologic wounds on the penis, perineum, and scrotum are also ideal for such therapy after initial debridement.. The first report of negative pressure wound therapy (NPWT) was by Fleischmann et al., *Unfallchirg.* 1993; 96: 488-92. It has been FDA approved since 1995. To perform NPWT, place a sterile foam dressing into wound defect, followed by a non-collapsible fenestrated tubing exits foam parallel to skin, connected to vacuum pump. The open wound is then converted into controlled closed wound (adhesive transparent film dressing placed on top of foam). Machine settings are typically 125 mmHg of negative pressure continuously or cyclically (5 min on, 2 min off). Dressing changes are made every 48 hours or 3 x/ week.

NPWT helps wounds to close and heal by the following mechanisms: removal of excessive interstitial edema, decompresses small vessels and restores local blood flow; removes chronic wound fluids rich in matrix metalloproteinases (inhibit wound healing); mechanical deformation of cells, with foam collapse, traction forces perturb the cytoskeleton and stimulate fibroblast, endothelial cell and vascular smooth muscle cell proliferation. Contraindications to NPWT are: malignancy in the wound, tissue necrosis (large amounts) with scar (debride before starting VAC), untreated osteomyelitis, insufficient vascularity to sustain any wound healing, untreated malnutrition.

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PATHOLOGY**Adenoid Cystic/Basal Cell Carcinoma of the Prostate Strongly Expresses HER-2/neu**

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Adenoid cystic/basal cell carcinoma (ACBCC) is a rare neoplasm in the prostate. Definitive treatment is warranted, as among 19 patients previously reported by us, 5 had extraprostatic extension and 4 were metastatic. The HER-2/neu (c-erbB-2) gene has been reportedly overexpressed in adenoid cystic carcinomas in other organs, but its status in prostatic ACBCC was uncertain. Immunohistochemical staining and in situ hybridisation were carried out in 13 patients with ACBCC (11 from transurethral resection, 2 prostatectomy). One patient had metastasis to the lung. Citrate buffer and steam heat were used for antigen retrieval. Ten acinar adenocarcinomas of varying grades were also immunostained as controls. Protein and mRNA expression were 2+ to 3+ (of 3+) in all patients with ACBCC, compared to a breast cancer control with strong reactivity, whereas protein expression was noted in only one acinar carcinoma and mRNA expression was absent in all acinar carcinomas. Benign acini expressed HER-2/neu only in the basal layer. The finding of strong, consistent HER-2/neu expression in ACBCC suggests that treatment with Herceptin (trastuzumab) may be effective in patients with this rare tumour.

Editorial Comment

This is a rare tumor composed of prostatic basal cells. Due to few cases reported, it was considered that the tumor had indolent biologic potential and some authors called the lesion “adenoid cystic-like tumor of the prostate gland” (1). In 2003, Iczkowski et al. (2) published the largest series calling attention to the potential aggressiveness of this tumor requiring ablative therapy. From a total of 19 patients, 5 showed extraprostatic extension on radical prostatectomy and 4 (21%) metastases: liver (2 patients), lung (2 patients), bowel (1 patient), and corpus cavernosum (1 patient). It is worth mention that the PSA was normal in most of the patients. Only 5 patients had elevated serum PSA of 4.5 to 9.2 ng/mL. This is an important finding with implication in the biochemical monitoring post-prostatectomy.

Based on the fact that HER-2/neu (c-erb-2) gene has been reportedly overexpressed in adenoid cystic carcinomas in other organs, Iczkowski and Montironi studied the expression of this gene in prostate tissue of 13 patients previously reported. Based on the finding that adenoid cystic/basal cell carcinoma of the prostate strongly expresses HER-2/neu we hope that treatment with Herceptin (trastuzumab) may be effective in patients with this rare and aggressive tumor.

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Detection of Life-Threatening Prostate Cancer with Prostate-Specific Antigen Velocity during a Window of Curability

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Background: Prostate-specific antigen (PSA) level is typically used as a dichotomous test for prostate cancer, resulting in over diagnosis for a substantial number of men. The rate at which serum PSA levels change (PSA velocity) may be an important indicator of the presence of life-threatening disease.

Methods: PSA velocity was determined in 980 men (856 without prostate cancer, 104 with prostate cancer who were alive or died of another cause, and 20 who died of prostate cancer) who were participants in the Baltimore Longitudinal Study of Aging for up to 39 years. The relative risks (RRs) of prostate cancer death and prostate cancer-specific survival stratified by PSA velocity were evaluated in the three groups of men by Cox regression and Kaplan-Meier analyses. Statistical tests were two-sided.

Results: PSA velocity measured 10-15 years before diagnosis (when most men had PSA levels below 4.0 ng/mL) was associated with cancer-specific survival 25 years later; survival was 92% (95% confidence interval [CI] = 84% to 96%) among men with PSA velocity of 0.35 ng/mL per year or less and 54% (95% CI = 15% to 82%) among men with PSA velocity above 0.35 ng/mL per year ($P < 0.001$). Furthermore, men with PSA velocity above 0.35 ng/mL per year had a higher relative risk of prostate cancer death than men with PSA velocity of 0.35 ng/mL per year or less (RR = 4.7, 95% CI = 1.3 to 16.5; $P = 0.02$); the rates per 100,000 person-years were 1240 for men with a PSA velocity above 0.35 ng/mL per year and 140 for men with a PSA velocity of 0.35 ng/mL per year or less.

Conclusions: PSA velocity may help identify men with life-threatening prostate cancer during a period when their PSA levels are associated with the presence of curable disease.

Editorial Comment

PSA velocity may help monitor patients in a period of “watchful waiting”. Due to rising frequency of prostate cancer detected in clinical stage T1c a higher number of cases have criteria for “insignificant” cancer and patients may elect “watchful waiting”. The term “insignificant” is not proper because it may imply that the tumor is latent (dormant or indolent). Unfortunately there is no marker for the biologic behavior of prostatic adenocarcinoma. The best term is “minimal volume carcinoma” and some predictive criteria include absence of Gleason grade 4 or 5, a maximum of 2 cores showing tumor and no more than 50% of the area of the core involved. Clinical stage must be T1c and PSA density less than 0.15 ng/mL (1). During the period of “watchful waiting” besides PSA velocity, free/total PSA should also be monitored and, very important, an annual needle prostatic biopsy. The reason for the biopsy is to detect an eventual change in extension and/or Gleason grading.

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INVESTIGATIVE UROLOGY

Detrusor Quantitative Morphometry in Obstructed Males and Controls

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J Urol. 176: 2722-8

Purpose: We studied the usefulness of computer assisted morphometry for measuring detrusor muscle cell diameter and the connective tissue-to-smooth muscle ratio in patients with bladder outlet obstruction, acute urinary retention and a nonobstructed control group.

Materials and Methods: A prospective study was done in patients with bladder outlet obstruction undergoing transurethral prostate resection. Patients were divided into 33 with obstruction and 14 in acute urinary retention. A total of 15 males without obstruction undergoing transurethral prostate resection for bladder tumor formed the control group. Detrusor specimens were obtained during transurethral prostate resection. Detrusor muscle cell diameter was measured using light microscopy and a semiautomatic image analysis system. The connective tissue-to-smooth muscle ratio was automatically determined with computer assisted image analysis. Symptoms and urodynamic assessment were performed preoperatively and 6 months postoperatively.

Results: A total of 62 patients were included. The obstruction and acute urinary retention groups had a statistically higher detrusor muscle cell diameter and more fibrosis than the control group. Patients in acute urinary retention had more intrafascicular fibrosis (higher connective tissue-to-smooth muscle ratio at 40x magnification) than patients with obstruction. There were no differences in detrusor muscle cell diameter or interfascicular fibrosis (connective tissue-to-smooth muscle ratio at 10x magnification) between the obstruction and acute urinary retention groups. Detrusor muscle cell diameter correlated with symptom duration and functional recovery after transurethral prostate resection. Detrusor fibrosis correlated with preoperative detrusor pressure at maximum flow and postoperative compliance. Patients in acute urinary retention had fewer symptoms and higher residual volume. Other urodynamic parameters and their improvement after surgery were similar in the acute urinary retention and obstruction groups.

Conclusions: Morphometric differences in detrusor muscle cell diameter and the connective tissue-to-smooth muscle ratio were observed between controls and patients with obstruction. There is an increase in detrusor muscle cell diameter and fibrosis in bladder outlet obstruction and more intense intrafascicular collagen deposition in patients in acute urinary retention.

Editorial Comment

Previous studies suggested that bladder outlet obstruction could produce histological changes in detrusor muscle and extracellular matrix; nevertheless, the results have been contradictory, with some authors reporting increase in smooth muscle and collagen decrease, while others reported collagen increase.

The authors studied 33 patients with bladder outlet obstruction (BOO) due to benign prostatic hyper trophy (BPH) and 14 patients in acute urinary retention (AUR). A total of 15 males without obstruction undergoing transurethral prostate resection for bladder tumor composed the control group. The present paper reported that the detrusor muscle cell diameter correlated with symptoms. It was found a positive correlation between the increase in cellular diameter and symptoms duration. The authors also studied the urodynamic parameters and found that there was no correlation in the obstructed and acute urinary retention groups with the detrusor muscle cell diameter. The authors found hypertrophy and an increase in fibrosis in patients with BOO. In patients with obstruction, there were slightly morphometric differences between those with an episode of AUR, that is higher intrafascicular fibrosis. There were no urodynamic differences preoperatively and postoperatively.

In a recent study (1), we analyzed the detrusor extracellular matrix in samples taken from bladders of 10 patients who underwent transvesical prostatectomy for treatment of BPH. Control material was composed of 10 vesical specimens, removed during autopsies performed in cadavers of accident victims, with ages between 18 and 35 years (mean = 26 years). We found that the components of connective tissue (collagen and elastic system fibers) are increased in the detrusor muscle of patients with infravesical obstruction, when compared to controls.

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Dynamic Contrast Enhanced Magnetic Resonance Imaging as a Biological Marker to Noninvasively Assess the effect of Finasteride on Prostatic Suburethral Microcirculation

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J Urol. 2006; 176: 2299-304

Purpose: We assessed dynamic contrast enhanced magnetic resonance imaging as a biological marker of in vivo changes in microcirculation in the prostatic suburethral region.

Materials and Methods: A total of 12 male beagle dogs with spontaneous benign prostatic hyperplasia were randomly allocated to 1 control group and 1 finasteride (Merck and Co., Whitehouse Station, New Jersey) treated group. Two baseline dynamic contrast enhanced magnetic resonance imaging examinations and 3 followups were performed to assess prostate microcirculation. Treatment duration was 3 months. The pharmacokinetic parameters evaluated in prostatic suburethral areas were the maximum enhancement ratio in AU, time to maximum signal enhancement in minutes, amplitude in AU and the exchange rate constant in minutes⁽⁻¹⁾.

Results: After completion of the therapeutic regimen time to maximum signal enhancement was significantly longer in the finasteride group than in controls ($p < 0.01$). Amplitude and the exchange rate constant decreased 39% and 34%, respectively, in the finasteride group at the end of treatment, which significantly differed from results in the control group ($p < 0.05$).

Conclusions: Dynamic contrast enhanced magnetic resonance imaging is capable of noninvasively assessing the prostatic microcirculation changes induced by finasteride. Pharmacokinetic parameters show considerable promise to be biomarkers for the development of benign prostatic hyperplasia drugs such as 5 α -reductase inhibitors by the in vivo monitoring of microvascular changes. A relevant clinical application could be the pretreatment assessment of finasteride effectiveness to decrease perioperative bleeding at transurethral prostate resection and in treatment for hematuria.

Editorial Comment

During the last years we learned that finasteride could decrease prostatic bleeding, both in benign prostatic hyperplasia (BPH) and in transurethral resection of the prostate (TURP), and we have been using finasteride in

the clinical setting for these proposes. Nevertheless, the mechanism of finasteride action in stopping bleeding is still unknown.

The authors of the present paper used male beagle dogs to assess dynamic contrast enhanced magnetic resonance imaging as a biological marker of in vivo changes in microcirculation in the prostatic suburethral region. They found that subjects in the finasteride group had decreased microcirculation, as expressed by lower and slower contrast enhancement, and as quantified by increased Tmax, and decreased A and kep in the prostatic suburethral area. They concluded that finasteride would decrease the prostatic microcirculation and therefore diminish prostatic bleeding in BPH and TURP.

In a recent experimental paper, Canda et al. (1) evaluated the effects of finasteride on the vascular surface density (VSD), number of microvessels (NVES) and vascular endothelial growth factor (VEGF) expression of the rat prostate. After studying 19 adult rats, the authors found that the mean prostatic weights were decreased significantly in rats given finasteride ($p=0.0001$). On the other hand, finasteride does not seem to decrease VSD, NVES and VEGF expression at the level of the rat prostate. The effect of reduction of bleeding in BPH is more likely to be due to its effect on shrinking glandular hyperplasia, which might enhance vessel wall stability, rather than decreasing overall vascularity (1).

From these two papers, we can infer that the exact mechanism of action of finasteride on the prostatic vessels is still open to research and discussion.

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RECONSTRUCTIVE UROLOGY

Gender Specific Chronological and Morphometric Ssessment of Fetal Bladder Wall Development

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J Urol. 2006; 176: 2674-8

Purpose: To enhance our understanding of sonographically visible alterations in bladder wall thickness, we delineated phenotypic changes occurring in developing smooth muscle cells of the fetal and postnatal bladder with respect to gender specific differences.

Materials and Methods: Bladders of 30 male and 18 female fetuses and 4 stillborn infants were immunostained with an alpha-smooth muscle actin antibody. Morphological and morphometric assessment was performed with the assistance of an image analysis system.

Results: Alpha-smooth muscle actin expression in fetal bladder wall was detectable at 9 weeks of gestation. Bladder wall thickness and mean profile area of smooth muscle bundles increased significantly with advancing gestation, mediated by linear growth patterns. Fetal bladder wall development occurred uniformly, unrelated to gender.

Conclusions: Although the lower urinary tract emerges in a gender specific way, our results suggest that in normal fetal growth detrusor muscle formation proceeds independent of genital sex.

Editorial Comment

The current paper deals with histologic and morphometric assessment of 18 female and 30 male bladder specimens of human fetuses at 9 to 35 weeks of gestation. The findings underline the theory of those favoring a gender independent development of the lower urinary tract. At various times during fetal development no differences between male and female specimens of the muscular structure and configuration of the bladder was seen contrary to previous reports (1). Furthermore, the growth of the muscular bladder wall was linear with gestational age.

This is a very elegant study with nice fetal specimens and reveals several interesting aspects. Apart from the main conclusions outlined above it was also interesting to see that the bladder seems to develop relatively late compared to the gut. At 9 weeks, only immature smooth muscle cells were observed in the bladder whereas the bowel already demonstrated clearly visible inner and outer muscular layers. In addition, smooth muscle cells developed first in the ventral portion of the bladder close to the dome. One may speculate that this has something to do with the umbilical vessels.

Only through the development of the bladder the muscle bundles start to change their shape, direction and intermingling. Unfortunately we do not get any clue from this study when and how neural development starts.

With studies like that we get important information for further tissue engineering of the urinary bladder. We suppose that at the time of in vitro cultivation intermingling and growth may not be our major goal but that we somehow have to have functional and growth stimulations at the time of implantation, which will bring our cultivated smooth muscle cells to a structure, which resembles the native bladder.

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Miniature Intravesical Urethral Lengthening Procedure for Treatment of Pediatric Neurogenic Urinary Incontinence

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J Urol. 2006; 176: 2663-6

Purpose: Resistance to flow in a fluid conduit is proportional to tube length divided by the radius to the fourth power (Poiseuille's law). We report the results of a miniature intravesical urethral lengthening procedure where outlet resistance is increased by minimizing the diameter of the intravesical urethral tube.

Materials and Methods: Nine pediatric patients with preoperative intractable incontinence underwent the miniature intravesical urethral lengthening procedure along with continent catheterizable stoma (9 patients)

and bladder augmentation (8). The intravesical portion of the urethral lengthening was 3 cm (traditionally 6 cm), and the urethra was tubularized around an 8Fr feeding tube (traditionally a 16Fr catheter). After the tubularized caudal portion was tunneled under the trigone the cephalad part of the urethra was placed as an onlay to the posterior bladder wall without ureteral reimplantation.

Results: At a mean followup of 31 months (range 10 to 47) 8 patients reported dry intervals of 3 hours or more, with minor leak per urethra only if they were overdue on the catheterization schedule. Mean postoperative abdominal leak point pressure was 71 cm H₂O (range 28 to 116). Upper tracts were well preserved in all patients. One patient required bladder neck closure for intractable incontinence.

Conclusions: The miniature intravesical urethral lengthening procedure requires minimal bladder tissue and is easy to perform. It appears to be an effective alternative in bladder neck reconstructive techniques, avoiding the need for ureteral reimplantation due to its small size, while functioning as a pop-off valve when the bladder is overly full. This procedure should be avoided in patients who lack a trigonal bar.

Editorial Comment

The reconstructive surgeon strives to benefit the patient with improved surgical approaches. Urinary incontinence, especially in patients with a neurogenic bladder, presents a significant surgical challenge and requires high level of experience (1). The technique of Kropp further developed by Pippi-Salle demonstrated the step-by-step perfection of the more advanced approach with the presented MIULP technique. This technique refreshed specific aspects of current approaches and further developed thoughts that are reflected in the described modified technique. However, the surgeon's responsibility is continued with the surgeon's legacy and sense of duty through long-term patient follow-up.

On the one hand, the tunneling of the lengthened urethra reduces the chance of fistula development; however, on the other hand the smaller urethral diameter might cause difficulties during catheterization. In our experience, the majority of patients prefer to use a catheterizable stoma. With the improved concept of regular sterile intermittent catheterization, there is a significant reduction in urinary infections and stone occurrence today, which reduces the chance of an endoscopic surgical approach.

The increased leak point pressure meets the patient's request to be dry and the "pop-off" valve makes allowance to limit the bladder pressure. With the introduction of Botulinum toxin, bladder augmentation can be often avoided or at least delayed securing the low-pressure storage (2).

This urethral lengthening technique might be a legitimate technique for the experienced surgeon to improve patient's long-term outcome.

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UROLOGICAL ONCOLOGY

Pathological Outcomes and Biochemical Progression in Men with T1c Prostate Cancer Undergoing Radical Prostatectomy with Prostate Specific Antigen 2.6 to 4.0 vs 4.1 to 6.0 ng/ml

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J Urol. 2006; 176: 554-8

Purpose: Recent studies have suggested that the cut point for recommending prostate biopsy among men with a normal digital rectal examination should be greater than 2.5 ng/ml as opposed to the more traditional greater than 4.0 ng/ml. We compared outcomes between men with clinical stage T1c disease undergoing radical prostatectomy who had a low vs slightly increased prostate specific antigen.

Materials and Methods: The study population consisted of 2,896 men treated with radical prostatectomy between 1985 and 2004 at a tertiary care referral center with clinical stage T1c disease and a pre-biopsy prostate specific antigen between 2.6 and 6.0 ng/ml. Using multivariate analysis we evaluated the association between pre-biopsy prostate specific antigen 2.6 to 4.0 ng/ml (784) vs 4.1 to 6.0 ng/ml (2,112), and pathological outcomes and biochemical progression.

Results: After adjusting for multiple clinical and pathological characteristics, lower preoperative serum prostate specific antigen values were associated with decreased odds of Gleason score 7 or greater in the surgical specimen ($p = 0.004$), positive surgical margins ($p = 0.02$) and extraprostatic extension ($p = 0.001$). There was no significant association between these preoperative prostate specific antigen groups and odds of seminal vesicle invasion ($p = 0.47$) or lymph node metastasis ($p = 0.90$). Among the 1,534 men with followup information available there was a trend for increased risk of biochemical progression associated with a higher preoperative prostate specific antigen, although this trend did not reach statistical significance (relative risk 1.48, 95% CI 0.69-3.19, $p = 0.31$).

Conclusions: In the current study of men with clinical stage T1c treated with radical prostatectomy a lower preoperative prostate specific antigen was associated with significantly more favorable pathological findings. Whether this degree of improved outcomes justifies the limitations associated with decreasing the prostate specific antigen cut point (e.g. increased biopsies performed and diagnosis of insignificant cancers) remains to be determined.

Editorial Comment

The authors focus on a rather large series of patients with a low serum PSA and biopsy-confirmed prostate cancer undergoing radical prostatectomy. Indeed, 784 patients with a PSA between 2.6 and 4.0 ng/mL were compared to patients with a PSA between 4.1 and 6.0 ng/mL. I wonder how suspicion of prostate cancer was generated in the first group, e.g. by abnormal digital examination?

Nevertheless, the results are interesting and give support to the notion that prostate cancer is an aggressive disease, even with low PSA. Positive surgical margins and capsular penetration were found in 6% and 14%, respectively, in the first group and in 9% and 21% in the higher PSA group. Recurrence-free survival was inferior after 10 years in the elevated PSA group.

What does that mean for the practicing urologist? To my opinion: detect and treat prostate cancer as early as possible.

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Long-Term Followup of a Randomized Study of Locally Advanced Prostate Cancer Treated with Combined Orchiectomy and External Radiotherapy versus Radiotherapy Alone

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J Urol. 2006; 176: 544-7

Purpose: In a randomized study we compared the combination of orchiectomy and radiotherapy to radiotherapy alone as treatment for locally advanced prostate cancer. Patients who were treated only with radiotherapy initially underwent castration therapy at clinical progression, providing the opportunity to compare immediate vs deferred endocrine intervention.

Materials And Methods: In this prospective study 91 patients with locally advanced prostate cancer were randomized to receive external beam radiotherapy (46) or combined orchiectomy and radiotherapy (45) after surgical lymph node staging. Survival rates were calculated.

Results: During 14 to 19 years of followup 87% of the patients in the radiotherapy group and 76% in the combined orchiectomy and radiotherapy group died (log rank $p = 0.03$). Prostate cancer mortality was 57% and 36%, respectively (log rank $p = 0.02$). The difference in favor of combined treatment was mainly caused by lymph node positive tumors. For node negative tumors there was no significant difference in the survival rates.

Conclusions: Immediate androgen deprivation should be considered instead of deferred endocrine treatment started at clinical progression for prostate cancer with spread to regional lymph nodes. While awaiting evidence from randomized trials, one should consider full dose radiotherapy for local control of locally advanced prostate cancer even when it is lymph node positive.

Editorial Comment

This paper gives the long-term results of a simple but well-done trial: immediate or deferred hormone ablative treatment in patients undergoing external beam radiation therapy (ERBT) after surgical lymph node staging.

The answer is clear-cut: immediate hormone ablative therapy is better than deferred therapy with regard to survival. This difference was most predominant in lymph node positive patients. In conclusion, these data and other papers strongly support the use adjuvant endocrine treatment in radiotherapy against prostate cancer.

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NEUROUROLOGY & FEMALE UROLOGY

Transurethral Radiofrequency Energy Collagen Micro-Remodeling For the Treatment of Female Stress Urinary Incontinence

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Neurourol Urodyn. 2006; 25: 331-6

Aims: This prospective, randomized, controlled clinical trial was performed to demonstrate the 12 months safety and efficacy of transurethral radiofrequency energy (RF) collagen micro-remodeling in women with stress urinary incontinence (SUI).

Materials and Methods: Women with SUI, bladder outlet hypermobility, and leak point pressure (LPP) $>$ or $=$ 60 cmH₂O were randomized to RF micro-remodeling or “sham treatment.” Adverse events (AEs) were recorded. Incidence of $>$ or $=$ 10 point incontinence quality of life (I-QOL) score improvement, a magnitude of improvement with a demonstrated responsiveness to patient satisfaction with treatment and to $>$ or $=$ 25% reduction in both incontinence episode frequency and stress pad weight, served as a subjective outcome measurement. Change in mean LPP served as an objective outcome measurement.

Results: 110 women underwent RF micro-remodeling and 63 underwent virtually identical “sham treatment” (with the exception of RF delivery). The 12 months RF micro-remodeling safety profile was statistically no different than that of sham treatment (a brief bladder catheterization). Seventy-four percent of women with moderate to severe baseline SUI experienced $>$ or $=$ 10 point I-QOL score improvement at 12 months ($P = 0.04$). Women who underwent RF micro-remodeling demonstrated LPP elevation at 12 months, while sham treated women demonstrated LPP reduction ($P = 0.02$).

Conclusions: Non-surgical, transurethral RF micro-remodeling is a safe treatment for women with SUI. In women with moderate to severe SUI, this novel therapy resulted in statistically significant improvement in quality of life of a magnitude associated with patient satisfaction with the treatment. Women who underwent RF micro-remodeling demonstrated a statistically significant elevation in mean LPP at 12 months.

Editorial Comment

In a well-constructed scientific study, the authors describe and analyze a technique to address female stress urinary incontinence utilizing radiofrequency energy to denature collagen in multiple microscopic sites causing a change in the compliance of the tissue. This anatomic change will theoretically reduce the inappropriate opening of the bladder neck and proximal urethra with stress maneuvers much in the manner of the sub urethral support of a sling. The technique utilizes less energy than that used by radiofrequency tissue ablation for renal masses and/or gynecological conditions. During the study, the authors used the Incontinence Quality of Life questionnaire (I-QOL) to grade the patient’s incontinence (as opposed to pad weight test) as well as urodynamics including leak point pressure determination. These metrics did make it a little challenging to note if any of the patients were absolutely dry post procedure. Nevertheless, treated patients were able to exhibit a statistically significant increase in leak point pressure at the 12-month follow-up period as opposed to those patients who underwent a sham treatment thus indicating a measure of efficacy (1). This study does speak volumes to the effect of placebo therapy for at the 12-month period almost 50% of both treated and sham groups had a $>$ 10 point I-QOL score improvement. The authors do clearly hi-light the safety and tolerability of this procedure and denote that radiofrequency micro remodeling clearly responds to the incontinent patients who will settle for improvement as opposed to cure in a trade-off for having a minimally invasive procedure. Similar patient desires with regards to injectable therapy have been noted in this journal (2).

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Vaginal Discharge and Bleeding in Girls Younger than 6 Years

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J Urol. 2006; 176: 2632-5

Purpose: Persistent unexplained vaginal discharge or bleeding in the pediatric population may be the only manifestation of a serious underlying medical or social problem. Therefore, these symptoms require careful and complete evaluation to identify the primary pathology accurately. We retrospectively reviewed charts of patients who presented for evaluation of persistent vaginal discharge or bleeding to determine if noninvasive imaging was a sensitive means of screening for gynecological pathology.

Materials and Methods: The records of 24 girls younger than 6 years who presented with vaginal discharge or bleeding were reviewed retrospectively. All patients were evaluated with noninvasive imaging, a pelvic examination while under anesthesia, vaginotomy and cystoscopy.

Results: Noninvasive imaging was useful in identifying 5 of 7 vaginal foreign bodies. However, noninvasive imaging identified only 2 of 6 malignancies. These malignancies consisted of rhabdomyosarcoma (3 patients) and endodermal sinus tumor (3). Two girls also had benign vaginal mullerian papillomas that were not identified by noninvasive imaging. Noninvasive imaging did not aid in the diagnosis of sexual abuse.

Conclusions: Based on these data, we recommend that all girls younger than 6 years who present with persistent vaginal discharge or bleeding be evaluated with pelvic examination while under anesthesia, to be followed by vaginotomy and cystoscopy if no readily identifiable pathology is found by simple genital examination alone, regardless of the results of noninvasive imaging studies.

Editorial Comment

The authors reviewed the efficacy of non-invasive imaging (including abdominal x-ray, ultrasound, CT scan and MR of the pelvis) in the population of females younger than 6 years old who presented to their clinic with vaginal discharge and bleeding as opposed to a physical examination with potential endoscopy under anesthesia; in addition, notation was made of the diagnoses found after evaluation. The patients had for the most part already been treated with antibiotic therapy prior to presentation to the authors. The study found that approximately half of the patients with vaginal discharge had a vaginal vault foreign body while one-third of the patients had no identifiable cause of the discharge. Of the patients with vaginal bleeding, almost half had a vaginal malignancy while approximately 15% had a foreign body within the vagina. The authors thus highlight the difference of potential diagnosis of vaginal discharge versus vaginal bleeding in this young population. Based on their findings, the presentation of vaginal bleeding in a female younger than 6 years old should engender an evaluation without hesitation under anesthesia since there is a high likelihood of the presence of malignancy.

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PEDIATRIC UROLOGY

Lack of Usefulness of Positioned Instillation of Contrast Cystogram after Injection of Dextranomer/Hyaluronic Acid

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J Urol. 2006; 176: 2654-6

Purpose: Positioned instillation of contrast cystograms have been touted as possibly being more sensitive than standard cystograms for evaluation of vesicoureteral reflux. We performed positioned instillation of contrast cystograms intraoperatively, immediately after the injection of dextranomer/hyaluronic acid to treat vesicoureteral reflux, to determine whether they might be predictive of operative success and obviate the need for the standard postoperative voiding cystourethrogram, which is usually performed at 3 months.

Materials and Methods: Patients with vesicoureteral reflux and no confounding conditions were treated with dextranomer/hyaluronic acid and subsequent positioned instillation of contrast cystogram while under the same anesthesia between November 2003 and March 2005. The results of this intraoperative cystogram were compared to the results of the postoperative voiding cystourethrogram performed 3 to 4 months later.

Results: A total of 61 patients met the inclusion criteria and underwent positioned instillation of contrast cystogram after dextranomer/hyaluronic acid injection. Only 53 patients (86 ureters) completed the necessary postoperative evaluation. Positioned instillation of contrast cystogram added 4 minutes to the procedure and required about 4 seconds of fluoroscopy per ureter evaluated. The overall success rate for correcting reflux was 84% (72 of 86 ureters cured). None of the 14 ureters with persistent postoperative reflux was identified by intraoperative cystogram, and 3 patients were misidentified as having reflux despite cure confirmed postoperatively. Intraoperative positioned instillation of contrast cystogram was predictive of treatment failure 0% of the time (sensitivity 0%). There were no complications.

Conclusions: Positioned instillation of contrast cystogram performed immediately after injection of dextranomer/hyaluronic acid was not useful in predicting which patients would have persistent reflux postoperatively. Patients are best served with the extant protocol of conventional cystography 3 to 4 months postoperatively.

Editorial Comment

This study is an ingenious attempt to improve the efficacy of endoscopic Dx/HA injection for the treatment of vesicoureteral reflux. The authors proposed that by doing a "PICC" study intraoperatively they could identify those patients who were going to fail endoscopic treatment (and in theory they could re-treat them at the same setting). Furthermore, if they could predict those who would ultimately fail with certainty, they could avoid an uncomfortable postoperative cystogram. Unfortunately, their idea did not prove effective.

Despite verbal reports to the contrary, correction of reflux in patients with endoscopic Dx/HA is effective in only 70-80% of patients on the first attempt. In this paper, as in many, the results were reported in terms of % ureters corrected. In this case it was 72 of 86 (84%). But of course patients and parents are much more concerned with the individual patient being cured of their reflux. In this study, reading between the lines, 14 of 53 patients had persistent reflux (in other words, 74% of patients were cured at 3 months). I believe this is typical of the results of most centers.

The idea of finding reflux on an intraoperative test that could result in immediate correction of the problem is great. Similarly, a study that would allow avoidance of a postoperative VCUG would be great. However, the composition of Dx/HA is such that the HA is absorbed over time. Hence, the size of the implant is very likely to get smaller with time. This makes it likely that patients that do not demonstrate reflux at the

time of the procedure, may well demonstrate reflux later, as the implant shrinks. What was interesting in this case was the fact that 3 patients had reflux demonstrated with PICC studies, but these same 3 did not show reflux at the later study. In this case, PICC appeared to be overly sensitive. Of course all types of cystograms miss about 20% of patients with reflux. Perhaps more important, the clinical course of these patients is not known, hence we really do not know whether the PICC study was clinically relevant or not or most important, whether the patients successfully treated with Dx/HA did better than those who failed. Much more work needs to be done in this area.

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Preoperative Anxiety, Postoperative Pain, and Behavioral Recovery in Young Children Undergoing Surgery

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Objective: Findings from published studies suggest that the postoperative recovery process is more painful, slower, and more complicated in adult patients who had high levels of preoperative anxiety. To date, no similar investigation has ever been conducted in young children.

Methods: We recruited 241 children aged 5 to 12 years scheduled to undergo elective outpatient tonsillectomy and adenoidectomy. Before surgery, we assessed child and parental situational anxiety and temperament. After surgery, all subjects were admitted to a research unit in which postoperative pain and analgesic consumption were assessed every 3 hours. After 24 hours in the hospital, children were discharged and followed up at home for the next 14 days. Pain management at home was standardized.

Results: Parental assessment of pain in their child showed that anxious children experienced significantly more pain both during the hospital stay and over the first 3 days at home. During home recovery, anxious children also consumed, on average, significantly more codeine and acetaminophen compared with the children who were not anxious. Anxious children also had a higher incidence of emergence delirium compared with the children who were not anxious (9.7% vs 1.5%) and had a higher incidence of postoperative anxiety and sleep problems.

Conclusions: Preoperative anxiety in young children undergoing surgery is associated with a more painful postoperative recovery and a higher incidence of sleep and other problems.

Editorial Comment

The authors studied the relationship between preoperative anxiety and recovery in a large series of children undergoing tonsillectomy and adenoidectomy. They show clearly that higher levels of preoperative anxiety are associated with increased postoperative morbidity, including more pain, use of more pain medication and less sleep. The differences between the more anxious and less anxious group resolved in about 3 days.

This study is unique in that it is the only study of its kind in children. Its message is important to those of us doing surgery on children. Based on these results, it suggests the hypothesis that reducing preoperative

anxiety will lead to better outcomes in the immediate postoperative period. Hence, better preoperative preparation may yield better outcomes.

Although this result is something most pediatric urologists would support intuitively, there are some issues with the study. First, all patients had a preoperative visit to the hospital. This is not usually done for minor surgical procedures. Would this have lessened or heightened the anxiety? More important, the study design prohibited the use of preoperative sedation or parents entering the operating room with the child (except in extreme cases). Though good for the study design, this is not typical in the real world. Nearly all our patients get preoperative sedation. Would the high anxiety patients have done better if they had the benefit of preoperative sedation with an amnesic? One would guess so. Further, for purposes of the study, all patients were admitted for 24 hours postoperatively. This is not typical of the procedure that was done and might also have increased the anxiety in those patients with high anxiety to start with.

Overall, the study is fascinating and tends to agree with common perception. However, more work needs to be done to evaluate whether education and/or pharmacological interventions, which are commonly accepted as standard of care, are truly successful in improving the postoperative course of children undergoing surgery and/or whether selected populations of those most anxious would benefit even more than others.

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Urothelial-Type Adenocarcinoma of the Prostate Mimicking Metastatic Colorectal Adenocarcinoma

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ABSTRACT

Adenocarcinoma arising in urinary bladder or prostatic urethra is uncommon. When they occur, the tumor can be mistaken for metastatic lesions, especially from the colon. Here we report the fifth case of a primary urothelial-type adenocarcinoma arising in the prostate which showed enteric differentiation. The patient was a 55 year-old male whose prostatic needle core biopsy showed a high grade adenocarcinoma which was initially thought to be metastatic colon cancer. A follow-up colonoscopy was unremarkable. Subsequent prostatectomy revealed a high grade adenocarcinoma which was positive for cytokeratins 7 and 20, carcinoembryonic antigen, CDX2, and high molecular weight cytokeratin, and negative for prostate specific antigen, prostate specific acid phosphatase and AMACR. A diagnosis of urothelial-type adenocarcinoma of the prostate was rendered. We review the literature regarding this entity, and discuss the differential diagnosis, emphasizing utility of immunohistochemistry in making the diagnosis. Finally, we speculate on the behavior of these rare tumors.

Key words: prostate; urothelial-type adenocarcinoma; pathology
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INTRODUCTION

Urothelial-type adenocarcinomas with mucinous/enteric differentiation arising in the prostatic gland is exceedingly rare, with only 4 case reports found in the literature. Tran & Epstein (1) described 2 cases of mucinous adenocarcinoma of urethral type which occurred in the setting of urethritis glandularis and associated adenocarcinoma in situ. Curtis et al. (2) described 2 additional cases in which both were centered around the prostatic urethra but were not associated with urethritis glandularis. The authors discussed the utility of immunohistochemistry in distinguishing these tumors from other histologic mimickers including conventional prostatic

adenocarcinoma and metastatic colorectal adenocarcinoma (2).

Here we report a case of rare urothelial-type adenocarcinoma with enteric differentiation arising in the prostate. The initial biopsy was suggestive of metastatic colorectal carcinoma to the prostate. We describe the clinicopathologic features and discuss the importance of immunohistochemistry in differentiating these two entities.

CASE REPORT

A 55 year old male presented to the urology clinic at our institution with a serum prostate-specific antigen (PSA) of 10.0 ng/mL and abnormal digital

rectal examination. Past medical history included hypertension and gout. The patient denied alcohol intake and quit smoking 10 years prior. The patient subsequently underwent a prostatic needle core biopsy which showed prostatic acinar adenocarcinoma, Gleason's grade 3+3 in 2 of 4 cores (30% of examined tissue) from the right lobe. In addition, the presence of high grade adenocarcinoma morphologically similar to colonic adenocarcinoma was observed in the left lobe. Based on the pathologic suspicion of metastatic colon cancer, a complete work-up was conducted to locate a primary colon cancer. An MRI of the pelvis showed diffuse involvement of the peripheral zone of left prostate gland (apex to base) with extension across the midline and possible extension to the left seminal vesicle. The patient subsequently had an unremarkable colonoscopy and negative colonic biopsy. A bone scan failed to reveal any metastatic tumor at that time. The patient underwent a retropubic radical prostatectomy with pelvic lymph node dissection for the prostatic acinar adenocarcinoma.

PATHOLOGIC FINDINGS

Gross

The radical prostatectomy specimen weighed 92 grams and measured 8.0 x 7.0 x 4.5 cm. The right seminal vesicle measured 2.5 x 2.0 x 1.4 cm, and the left seminal vesicle measured 1.0 x 1.0 x 0.7 cm. The external surface of the prostate was tan with a shaggy appearance. Serially sectioning from apex to base revealed a large, tan-white, firm and focally necrotic, infiltrative mass lesion measuring 3.5 x 3.0 x 2.0 cm, replacing almost the entire left lobe. This mass grossly extended into the capsule and the left seminal vesicle. The remaining cut surface of the prostate had a tan nodular appearance without additional discernable tumors.

Microscopic

Hematoxylin and eosin (HE) stained sections from both the left needle core biopsy and prostatectomy specimens showed a high grade

adenocarcinoma with glandular and cribriform architecture infiltrating the prostatic parenchyma (Figure-1). Abundant "dirty-type" necrosis within malignant glandular structures, characteristically seen in colonic-type adenocarcinoma, was identified (Figure-2). The tumor cells were columnar to polygonal with high nuclear to cytoplasmic ratios, marked pleomorphism, and prominent nucleoli

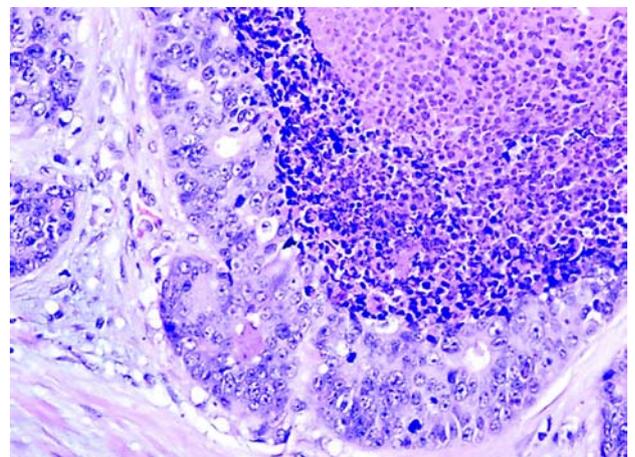


Figure 1 – Prostatectomy with high-grade adenocarcinoma with glandular and cribriform architecture (HE, X400).

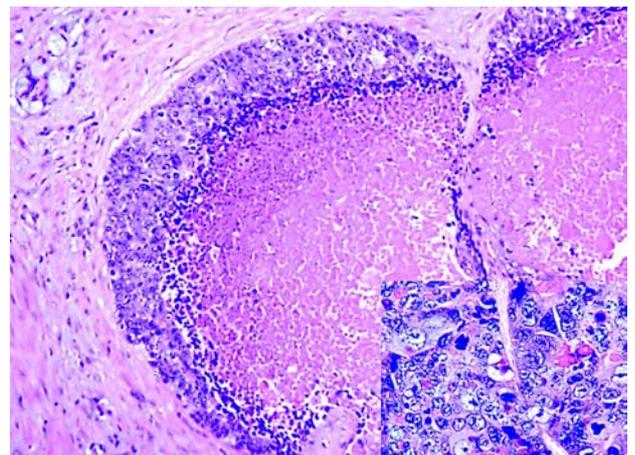


Figure 2 – Abundant "dirty-type" necrosis characteristically seen in colonic-type adenocarcinoma was identified within many malignant glands (HE, X200). Note the small focus of conventional prostatic acinar adenocarcinoma in upper left corner. The tumor cells were columnar to polygonal with high nuclear to cytoplasmic ratios, marked pleomorphism, prominent nucleoli and numerous mitosis (Inset, HE, X400).

(Figure-2, inset). They displayed abundant mitotic activity and apoptosis. No intracellular or extracellular mucin was identified. The morphology seen on the H&E stains was very reminiscent of a high grade enteric-type adenocarcinoma. The tumor was predominantly present on the left side, with extensive extraprostatic extension and focally positive margins. Perineural as well as vascular invasion was also identified. The tumor involved approximately 90% of the left lobe and 10% of the right lobe of the gland. It also extended into both seminal vesicles microscopically. Both left and right pelvic lymph nodes sampled were negative for metastatic tumor.

A second population of tumor cells was present in both the right side core biopsy and prostatectomy specimens, mostly in the right lobe. It consisted of infiltrating acinar structures composed of uniform cuboidal cells with prominent nucleoli, morphologically characteristic of conventional prostatic acinar adenocarcinoma, Gleason's score 4+3 (Figure-3). The tumor was a minor component in the prostatectomy specimen occupying less than 5% of the total gland volume and was in close proximity to the enteric type adenocarcinoma.

Immunohistochemistry for cytokeratin 20 (CK20), prostate-specific antigen (PSA), and CDX2 were performed on the right-sided core biopsy containing the high grade adenocarcinoma reminiscent of colonic adenocarcinoma. The tumor was diffusely and strongly positive for CK20 and CDX2 and negative for PSA. This led to the suspicion of metastatic poorly differentiated adenocarcinoma consistent with colonic primary on prostatic biopsy specimen.

Furthermore, a panel of immunohistochemical stains for cytokeratin 7 and 20, PSA, PSAP, thrombomodulin, alpha methylacyl CoA racemase (AMACR), CDX2, monoclonal carcinoembryonic antigen (mCEA), CD31, human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), placental alkaline phosphatase (PLAP), and high-molecular weight keratin (HMWK) were performed on sections from the prostatectomy specimen. The high grade adenocarcinoma showed strong diffuse expression of CK20, CDX2, and HMWK as well as

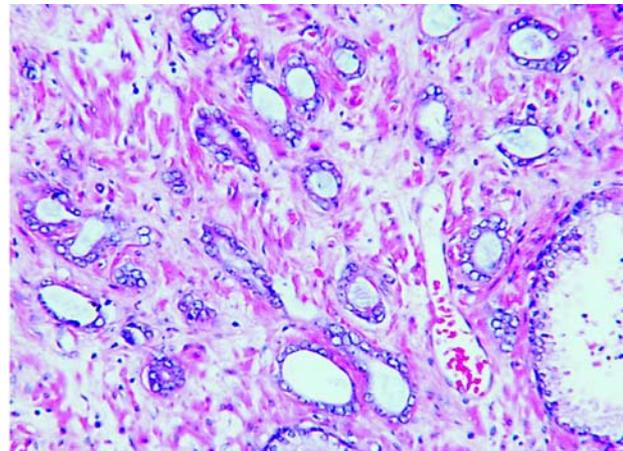


Figure 3 – Infiltrating acinar structures composed of uniform cuboidal cells with prominent nucleoli, morphologically consistent with prostatic acinar adenocarcinoma (HE, X200).

focal expression of CK7 and mCEA. The tumor was completely negative for PSA, PSAP, thrombomodulin, AMACR, CD31, AFP, and PLAP. Less than 1% of cells were positive for HCG. The immunostaining results are summarized in Table-1 and partially illustrated in Figure-4 and 5.

COMMENTS

Within the prostate gland, urothelium lines primarily the prostatic urethra but may extend to portions of major prostatic ducts. Even prostatic acini can undergo urothelial (transitional) metaplasia. Theoretically, any lesion which is known to occur elsewhere in the urothelial tract may occur in the prostate gland, and urothelial lesions such as inverted papilloma and urothelial carcinoma have all been described in the prostate (3-5). Adenocarcinoma, a tumor usually occurring in the bladder or urethra, can assume patterns similar to colonic adenocarcinoma including the typical enteric pattern, signet-ring pattern, and mucinous pattern (6,7). It is suggested that adenocarcinoma of bladder or urethra usually arises in precursor lesions like urethritis glandularis (1) or periurethral structures such as Cowper's glands. Urothelial-type adenocarcinoma arising in the prostate is exceedingly rare, with only four previous cases reported in the literature.

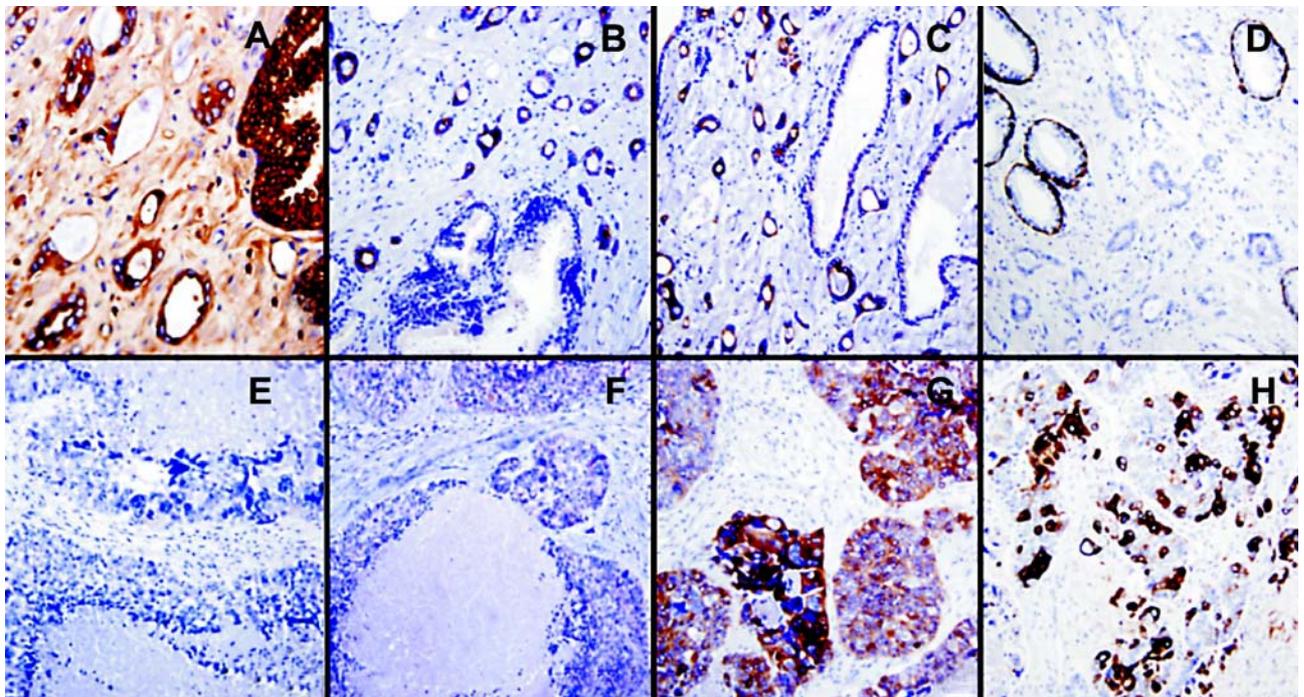


Figure 4 – Immunohistochemical results in conventional prostatic acinar adenocarcinoma (A-D) and urothelial-type adenocarcinoma in prostatectomy specimen. The conventional acinar adenocarcinoma was positive for PSA (A), AMACR (B), and CK7 (C), but negative for HMWCK (D). The urothelial-type adenocarcinoma was negative for PSA (E) and AMACR (F) but positive for CK7 (G) and HMWCK (H), Immunolabelling, X400.

The differential diagnosis for urothelial-type adenocarcinoma of the prostate includes prostatic mucinous adenocarcinoma, prostatic ductal adenocarcinoma, and metastatic colonic

adenocarcinoma. Mucinous adenocarcinoma of the prostate typically has cribriform glands with bland cytology characteristic of conventional prostatic acinar adenocarcinoma. These tumors are typically

Table 1 – Summary of immunohistochemical results for urothelial-type adenocarcinoma and prostatic acinar adenocarcinoma.

Antibody	Company	Dilution	Urothelial-Type Adenocarcinoma	Prostatic Acinar Adenocarcinoma
AMACR	Zeta Co.	1:100	negative	positive
CDX2	Biogenex	1:20	positive (weakly)	negative
CK7	Dako	1:100	positive (focally)	positive (focal)
CK20	Dako	1:25	positive	positive (focal)
HMWCK	Dako	1:50	positive	negative
CEA	Dako	1:100	positive	negative
HCG	Dako	1:25	positive (1% cells)	negative
PSAP	Dako	1:50	negative	positive
PSA	Dako	1:1800	negative	positive

AMACR = alpha methylacyl CoA racemase; CK = cytokeratin; HMWCK = high molecular weight cytokeratin; CEA = carcinoembryonic antigen; HCG = human chorionic gonadotropin; PSAP = prostate-specific acid phosphatase; PSA = prostate-specific antigen.

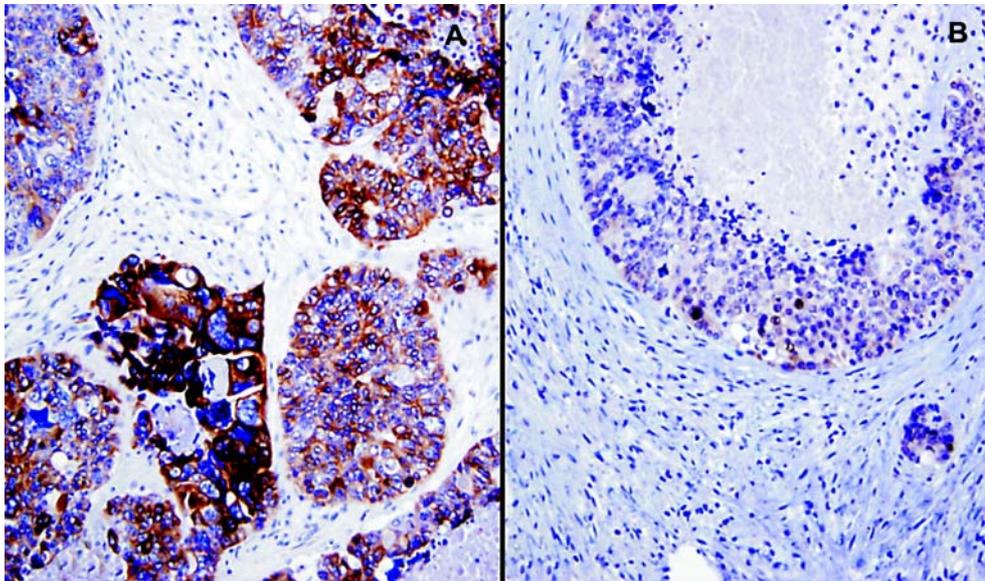


Figure 5 – Similar to colorectal adenocarcinoma, the urothelial-type adenocarcinoma was diffusely positive for CK20 (A) and CDX2 (B), Immunolabelling, X400.

intermingled with conventional acinar adenocarcinoma, and usually classified as Gleason score 3+4. The epithelium may float in mucin and the cells express PSA and PSAP (8). Ductal adenocarcinomas of the prostate may very closely resemble urothelial type adenocarcinoma but are also positive for PSA and PSAP (9).

Perhaps the most challenging differential diagnosis is that of metastatic colorectal adenocarcinoma, which can look almost identical to urothelial-type adenocarcinoma. Immunohistochemistry can be helpful in these situations as we previously reported (10). Cytokeratin 7 (CK7) is typically positive in urothelial carcinoma but negative in colorectal carcinoma (10), although both tumors are positive for cytokeratin 20. In this case, tumor cells were focally positive for CK7. Villin, reported to be positive in colonic adenocarcinoma and negative in urothelial carcinoma with glandular differentiation, has been shown to be expressed in enteric-type urothelial adenocarcinoma (11). High molecular weight keratins, including CK 1, 5, 10 and 14, have been shown to be highly expressed in urothelial carcinomas and only rarely expressed in colonic and prostatic adenocarcinomas (12). It has also been

reported that HCG producing tumor cells can be seen in urothelial carcinoma.

AMACR was first identified as a prostate cancer marker (13). Further studies showed its expression in the majority of colonic adenocarcinomas (14). In addition, AMACR is also positive in prostatic mucinous adenocarcinoma and ductal adenocarcinoma, although the reactivity may be reduced focally. AMACR is typically negative or weakly positive in urothelial carcinoma and positive in a small percentage of adenocarcinomas of the bladder (15). The negative AMACR stain in this high grade urothelial-type adenocarcinoma supports its urothelial differentiation and is inconsistent with prostatic ductal adenocarcinoma or colonic adenocarcinoma. In the case reported here, the finding of a small subset of HCG positive cells also supports the urothelial origin or differentiation of this tumor.

Curtis et al. (2) proposed that a panel of antibodies to PSA, PSAP, CK7, CK20 and HMWK would be useful in differentiating urothelial-type adenocarcinoma, metastatic colorectal adenocarcinoma, and conventional prostatic acinar adenocarcinoma. Urothelial-type adenocarcinomas should be positive for HMWK and CK7 and may be

positive for CK20, but should not express PSA and PSAP. Colorectal carcinoma should be positive for CK20 but negative for all other markers. Prostatic acinar or ductal adenocarcinoma should express PSA and PSAP but be negative for all other markers. Our tumor strongly expressed CK20 and CEA, and was focally positive for CDX2. This profile may suggest a colorectal primary. However, our tumor also expressed HMWK and CK7, which is not typical of colon cancer. More importantly, the patient had a completely negative workup for primary colon cancer. Hence we feel that our case is most consistent with urothelial-type adenocarcinoma of the prostate gland showing a degree of enteric differentiation. Although our tumor did not contain mucin, it had other characteristics commonly seen in colorectal carcinoma including extensive dirty necrosis and a focal cribriform growth pattern.

The etiology of this malignant tumor is unknown. Although urethritis glandularis has been proposed to be a precursor lesion for urothelial-type adenocarcinoma, our patient did not have evidence of urethritis glandularis. In fact, the sampled prostatic urethral mucosa was histologically unremarkable. One possibility is that the tumor arose from a prostatic duct, which may be lined by urothelial-type mucosa. Of interest, our patient also had a small focus of conventional acinar-type prostatic adenocarcinoma, which was also described in two of the four previous case reports. Therefore, an alternative possibility is that this tumor may be derived from a stem cell which underwent biphasic differentiation to urothelial-type adenocarcinoma and conventional prostatic acinar adenocarcinoma.

Due to the rarity of these tumors, it is difficult to predict their behavior. One previously reported patient died of disease with liver metastasis within one year of initial diagnosis (2). Another patient experienced local recurrence 4 years status-post simple prostatectomy (1). The two other patients showed no evidence of disease one year¹ and 16 months (2) status-post radical prostatectomy. Our patient developed both local recurrence as well as multiple metastases to lung, liver, and bone within 4 months of prostatectomy. It was observed that the metastatic tumors of this patient were morphologically

and immunohistochemically identical to the urothelial-type adenocarcinoma of the prostate. Therefore, it is important to note that these tumors may behave in an aggressive manner.

In conclusion, we have described a rare high grade urothelial-type adenocarcinoma arising in the prostate. This primary prostatic tumor, mimicking metastatic colorectal adenocarcinoma due to its striking morphologic resemblance as well as overlapping immunohistochemical phenotype, should be recognized for appropriate clinical management. Our study supports the previous notion that high molecular weight keratin may be the key marker for differentiating these tumors from colorectal metastasis.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This is a very well written paper on a very rare tumor. Adenocarcinoma of the urinary tract may correspond to 3 possibilities: glandular differentiation of a conventional urothelial carcinoma (more frequently), secondary

involvement (more frequently from the prostate or colorectal region), and primary (more rarely). Clinical work-up as well as morphology characteristics and immunohistochemistry help in the differential diagnosis.

Primary adenocarcinomas may also arise from the urethra or distal prostatic ducts. In this case the differential diagnosis is much more difficult because the great majority of the cases are conventional adenocarcinomas of the prostate and the pathologist is not aware of the possibility of dealing with a so rare condition. The differential must be done with a

thorough clinical work-up to exclude adenocarcinoma of the rectum or colon and, on morphology, only by immunohistochemistry.

Only 4 cases were previously published of a primary urothelial-type adenocarcinoma of the prostate. The final diagnosis is mainly based on immunohistochemistry.

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