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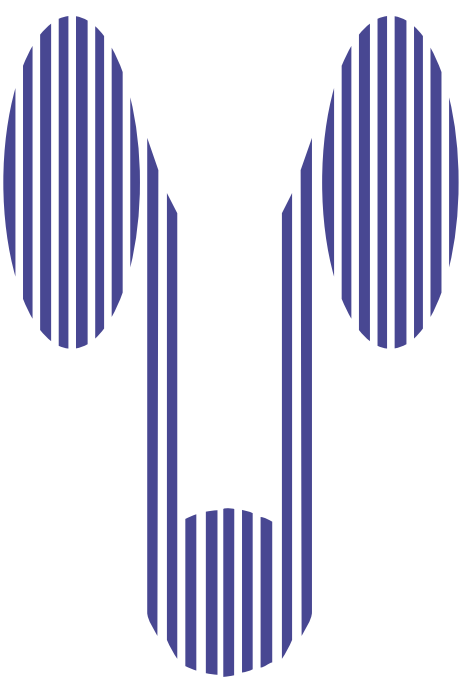

XXXI Brazilian Congress of Urology
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Penile Carcinoma – An Endemic Disease in Developing Countries

The January - February 2007 issue of the International Braz J Urol presents interesting contributions from different countries, and as usual, the editor's comment highlights some papers. Starting with this issue, the editor will choose the subject of an appealing article for title the editor's comment.

Doctor Gonzaga-Silva and co-workers, from Federal University and Cancer Hospital of Ceara, Brazil, studied on page 58 the results of the use of isolated gamma probe for sentinel node penile carcinoma detection and discussed the incidence of false negative rates. Impressive, during the last 5 years, the authors have been identified 3 new cases of penile carcinoma at the cancer hospital, every month. Twenty-seven newly diagnosed penile carcinoma patients (T1, T2, N0) were included in this prospective study. The authors found that isolated gamma probe technique for sentinel node penile carcinoma has a very low sensibility and a high false negative rate and concluded that this isolated technique is unreliable. Prominent experts and pioneers in the field, Dr Simon Horenblas, from the Netherlands Cancer Institute, Amsterdam, The Netherlands, Dr. Curtis A. Pettaway, from the M.D. Anderson Cancer Center, Houston, Texas, USA, and Doctors Dr. Riccardo Autorino, from Seconda Università and Dr. Sisto Perdonà from Istituto Nazionale Tumori, Napoli, Italy, provided excellent editorial comments on this paper, which deserve to be read by all urological oncologists.

Doctor Skalova and colleagues from Departments of Pediatrics and Radiology, Charles University in Prague, Czech Republic, measured on page 80 the urinary N-acetyl-beta-D-glucosaminidase (U-NAG) activity - U-NAG/creatinine ratio in 31 children with hydronephrosis grade 1-4. It was found that U-NAG/Cr was significantly higher in patients with hydronephrosis when compared to reference data, with no relationship with the grade of hydronephrosis. The authors concluded that the U-NAG is a useful marker of renal tubular dysfunction, however its relationship with the degree of kidney damage in patients with hydronephrosis should be considered as doubtful. Recognized experts, Dr. Y. Yang, from China Medical University, Shenyang City, China, Dr. Boris Chertin, from Shaare Zedek Medical Center, Jerusalem, Israel and Dr. David R. Vandersteen, from Mayo Graduate School of Medicine, Minneapolis, Minnesota, USA, provided editorial comments that give a critical analysis on the findings of this manuscript.

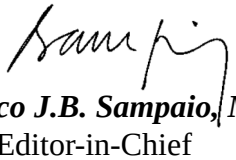
Doctor Shefi and collaborators, from University of California San Francisco, California, USA, evaluated on page 50 the recovery of semen quality in a cohort of infertile men after known hyperthermic exposure to hot tubs, hot baths or whirlpool baths. Eleven infertile men exposed to hyperthermia were evaluated pre and post-exposure. Five patients (45%) responded favorably to cessation of heat exposure and had a mean increase in total motile sperm counts of 491%. It was concluded that the toxic effect of hyperthermia on semen quality might be reversible in some infertile men. Also, it was observed that the seminal response to exposure elimination varies biologically among individuals and can be profound in magnitude. Among non-responders, other risk factors that could explain a lack of response to elimination of hyperthermia should be considered. Doctor Dr. Yefim R. Sheynkin, from State University of New York at Stony Brook, New York,

USA, provided editorial comment on this debatable article that was replied by the authors. I recommend all urologists involved in infertility treatment to read this manuscript.

Doctor Tabibi and associates, from Shahid Beheshti University of Medical Sciences, Tehran, Iran, presented on page 19 their results on a randomized clinical trial of percutaneous nephrolithotomy with and without retrograde pyelography. Fifty-five patients with opaque renal calculi were randomized into 2 groups, noncatheterized (n = 28) and catheterized (n = 27). No difference in outcome, postoperative fever, duration of surgery, duration of hospital stay and radiation exposure was observed between the 2 groups. Dr. Anuar I. Mitre, from Sao Paulo University Medical School, Brazil and Dr. Hassan A. Razvi, from University of Western Ontario, London, Ontario, Canada, provided editorial comments that give balance on the findings of this provocative article.

Doctor McLaughlin and co-workers, from The University of North Carolina at Chapel Hill, USA, retrospectively evaluated on page 25 patients undergoing radical cystectomy (RCx) with regard to pathologic outcomes and degree of upstaging to better identify features that may lessen clinical understaging. Of the 141 patients evaluated, 54% were upstaged on operative pathology. The greatest degree of upstaging occurred in those with invasive disease preoperatively (cT2-T3). Twenty-six percent of all patients had node-positive disease, and 75% of cT3 patients were node-positive. Seven of 101 (7%) patients with clinical T2 disease were unresectable at the time of surgery. Impressive, is the finding that in the more modern cohort, the degree of upstaging was not improved. The authors concluded that pathologic findings after RCx often do not correlate with preoperative staging. Over half of patients undergoing cystectomy are upstaged on their operative pathology. Dr. M. Manoharan, from the Bladder Cancer & Neobladder Center, University of Miami, Florida, USA, provided editorial comment on this article.

Doctor Romero and colleagues, form The Johns Hopkins Medical Institutions, Maryland, Baltimore, USA, described on page 94 an experimental work on a simplified experimental technique for total laparoscopic gastrocystoplasty in a porcine model. After performing laparoscopic gastrocystoplasty on 10 animals, the authors concluded that total laparoscopic gastrocystoplasty is a feasible but complex procedure that currently has limited clinical application. Dr. Jose R Colombo Jr., from the Section of Laparoscopic and Robotic Surgery, Cleveland Clinic Ohio, USA, commented on this article.



Francisco J.B. Sampaio, M.D.
Editor-in-Chief

Review Article
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Energy Sources for Laparoscopic Partial Nephrectomy - Critical Appraisal

Mauricio Rubinstein, Alireza Moinzadeh, Jose R. Colombo Jr, Luciano A. Favorito, Francisco J. Sampaio, Inderbir S. Gill

Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil, Section of Laparoscopic and Robotic Surgery, State University of New York, Syracuse, New York, USA, and Section of Laparoscopic and Robotic Surgery, Glickman Urological Institute, The Cleveland Clinic, Cleveland, Ohio, USA

ABSTRACT

Laparoscopic partial nephrectomy (LPN) has emerged as a viable alternative for the conventional open nephron-sparing surgery (NSS). So far, an adequate renal parenchymal cutting and hemostasis, as well as caliceal repair remains technically challenging. Numerous investigators have developed techniques using different energy sources to simplify the technically demanding LPN. Herein we review these energy sources, discussing perceived advantages and disadvantages of each technique.

***Key words**: laparoscopy; surgical procedures, minimally invasive; nephrectomy; energy sources*
Int Braz J Urol. 2007; 33: 3-10

INTRODUCTION

The majority of renal tumors are now incidentally diagnosed and smaller than 4 cm (1). The treatment of choice for most small renal masses is the NSS. Fergany et al. have demonstrated similar results comparing partial and radical nephrectomy for 10 year follow-up (2).

Although some different techniques of LPN have been described (3-7), in the senior author institution (ISG), this technique include complete kidney exposure, hilar clamping, cold cut with laparoscopic scissors, precise collecting system closure, reconstruction of partial nephrectomy bed over surgical bolsters, and the use of biological haemostatic agent (Floseal®).

Widespread application of LPN has been limited given the challenges associated with intracorporeal suturing for hemostasis and collecting system closure. To simplify the procedure, several reports have been published using various energy modalities to replace the need for intracorporeal suturing (6-8).

In this review, we describe and evaluate several energy sources used to achieve cutting and hemostasis during LPN, as well as ablative tissue energies, outlining the advantages and disadvantages of each one.

LASERS: CUTTING AND HEMOSTATIC ENERGY

Several lasers have been developed specifically for surgical applications, being used to cut or

vaporize tissue while leaving a coagulated field. Their efficacy to coagulate or excise tissue is regulated by specific wavelength, energy or power setting and mode of operation (continuous or pulsed) (8). Applications in urology include lithotripsy, ablation of bladder tumors, transurethral resection of prostate, and partial nephrectomy (9).

Several kinds of laser energy have been tested for parenchymal transection during LPN (8-11). The use of laser fibers with the specific application of tissue welding is based on delivering energy to the target lesion, with heat absorption resulting in thermocoagulation. This modality avoids needle trauma and suture reaction, may allow shorter operative time and less bleeding, although it presents thermal damage in tissue with indirect contact (12-15). The search for the ideal hemostatic method still continues since no single laser was proven to have ideal results.

Descriptions of open laser partial nephrectomy using the CO_2, Nd: YAG and holmium lasers have previously been published (10,16). Since this early experience, several authors have reported the use of lasers for LPN in animal model, as well as in the clinical field (Table-1). Lotan et al. (16) studied the use of holmium laser for partial nephrectomy in the porcine model. The authors performed transperitoneal lower pole laparoscopic partial nephrectomy in 5 pigs. Fibrin glue was applied to the nephrectomy bed to seal the collecting system. All cases were performed with adequate hemostasis and without the need of further hemostatic devices.

Lotan et al. (17) described the first clinical report of laser during LPN, using the holmium: YAG laser in three patients. Indications included complex cyst, nonfunctioning lower pole, and renal mass. There was minimal blood loss and no need for hilar clamping. Although the laser alone was hemostatic, the authors used fibrin glue in two cases and oxidized cellulose in one case to reinforce the tissue against delayed bleeding. There were no perioperative complications and the average hospitalization was 3 days. The authors in this study concluded that with high power settings (0.2J/pulse at 60 pulses/sec and 0.8J/pulse at 40 pulses/sec), the Ho: YAG laser can be used as an effective hemostatic tool in LPN.

The advantages of this laser are simplicity of use and relative low cost. The Ho: YAG laser is able to cut and coagulate tissues, with minimal damage to the adjacent renal parenchyma, preserving as much normal tissue as possible. The disadvantages include the smoke created and the splashing of blood on the camera, particularly when transecting larger vessels.

The use of Diode laser in LPN was reported by Ogan et al. (18). They performed transperitoneal lower pole laparoscopic partial nephrectomy in 5 pigs without the need for hilar occlusion using a 980-nm diode laser. The laser hemostasis was insufficient in 3 cases, requiring adjunctive measures, as hemostatic

Table 1 – *Use of laser during laparoscopic partial nephrectomy.*

Author/Year	Animal Model vs. Clinical (n)	Acute vs. Chronic	Open vs. Laparoscopic	Laser Employed	Hilar Clamping
Hughes (5), 1972	canine (n = 7)	chronic	open	CO_2	yes
Meiraz (7), 1977	feline (n = 20)	chronic	open	CO_2	yes
Benderev (49), 1985	canine (n = -)	chronic	open	Nd: YAG	yes
Landau (9), 1987	canine (n = 20)	acute	open	Nd: YAG	yes
Taari (10), 1994	porcine (n = 9)	acute	open	Nd: YAG	yes
Ogan (11), 2002	porcine (n = 5)	chronic	laparoscopic	Diode	no
Ogan (13), 2003	porcine (n = 5)	chronic	laparoscopic	Diode	yes
Moinzadeh (20), 2005	bovine (n = 6)	chronic	laparoscopic	KTP	no
Lotan (12), 2002	clinical (n = 3)	N/A	laparoscopic	Ho: YAG	no

**Adapted from Moinzadeh et al.: Potassium-titanyl-phosphate laser laparoscopic partial nephrectomy without hilar clamping in the survival calf model. J. Urol. 2005, 174: 1110-4.*

clips to stop bleeding. The mean operative time was 126 minutes, the mean blood loss was 150 mL (50-300 mL), and no urinary extravasation was observed on retrograde pyelogram at 2 weeks. The authors concluded that the diode laser is feasible on the porcine model and limited its use in humans to small periferic tumors. The limitation of this laser was observed in controlling large vessels. Fibrin glue was applied to all partial nephrectomies, resulting in selling of the collecting system in all cases. It was unknown if the selling occurred as result of the glue or the laser. Further studies are necessary to achieve success with this kind of energy in LPN.

The same group has utilized an 810-nm pulsed diode laser (20W) plus a 50% liquid albumin-indocyanine green solder in 5 pigs demonstrating the tissue welding qualities of lasers (19). All surgeries were performed without complications with mean operative time of 82 minutes. Average blood loss was 43.5 mL and mean warm ischemia time was 11.7 minutes. There was no evidence of urinoma formation or delayed hemorrhage in any of the animals. Histologic studies showed good preservation of renal parenchyma beneath the solder.

The main advantage of this soldering technique includes the ability to close the collecting system and control of bleeding during LPN, with short warm ischemia time (< 12 minutes). In this study, the laser was able to control large vessels, mimicking human LPN, and the violated collecting system was fixed with the solder without problems. Further studies are required to confirm this fact.

The KTP laser has been recently tested for LPN in the calf model (20). Using 6 calves, the authors successfully completed the operation without hilar clamping in 11/12 procedures. One animal required temporary occlusion of the hilum for hemorrhage not controlled with the laser. The histological analysis revealed minimal effect on the adjacent area to the excision. The unique feature of the KTP laser includes the 532-nm wavelength, with specific uptake by hemoglobin. The authors believed that this aspect yielded excellent hemostasis in the robust calf model. In addition, minimal blood splatter was noted given decreased bleeding and thermomechanical ejection when compared to the Ho:YAG laser.

HIDRO-JET DEVICE: MAINLY CUTTING ENERGY

Hydro-jet technology has been established for surgery of the liver and other parenchymatous organs, using the principle of high-pressure water flow to cut tissues (21,22). The delivery probe allows dissection with both water high pressure and blunt dissection. Coagulation is applied usually with a bipolar thermo-applicator if needed. The first report in the urologic field was done by Pentchev et al. for open renal surgery in the canine model (23).

Shekarriz et al. published the first experimental laparoscopic study in LPN. The authors performed the procedure with hilar clamping in the porcine model, using 5 animals (24). In this study, the mean warm ischemia time was 17 minutes. Moinzadeh et al. evaluated the feasibility of hydro-jet assisted LPN without renal hilar vascular control in the larger size and more robust calf model, to better reproduce the human kidney (25). The authors performed bilateral LPN using the Helix Hydro-Jet® (ERBE Tubingen, Germany) without hilar control in 10 survival calves. All procedures were completed successfully without open conversion, and the hilar clamping was not needed in 18 (90%) cases. The mean operative time was 173 minutes (60-240), kidney section time was 63 minutes (13-150), and estimated blood loss was 174 cc (20-750). Histological studies showed a thin (1 mm) layer of adherent coagulum beneath the resection area with minimal thermal artifact.

Clinically, Penchev et al. used the hydro-jet without hilar clamping in open partial nephrectomy for a low pole tumor (n = 1) and open anatrophic nephrotomy of a staghorn calculi (n = 1) (26). The hydro-jet dissection time was 25 and 12 minutes, with blood loss of 150 and 100 mL, respectively. The procedures were done without vascular clamping or local hypothermia (27).

Basting et al. reported the largest clinical experience with the hydro-jet device for a variety of open kidney procedures (26). A total of 24 patients underwent open surgery for nephrolithiasis, renal masses, and complicated cysts. Operative resection time was between 14 and 40 minutes with minimal intraoperative blood loss. They concluded that the

water jet device was useful for renal parenchymal transection.

To date, no clinical report of hydro-jet LPN has been published, but the suitability of the LPN technique to improve hemostasis and dissection has been proven (Table-2). This use of kinetic energy has the advantage of dissect selective parenchyma while preserving vessels and the collecting system during the surgery. With this technology, the procedure may be easier, faster, avoiding the warm ischemia and the technically challenging intracorporeal suturing during LPN. Since there is no cautery tissue damage, the Hydro-jet device preserves the renal parenchyma. Limitations include the theoretical spread of cancer cells with the use of the high pressure saline flow. In addition, current rigid instruments lacking flexibility make the laparoscopic angles of dissection challenging.

BIPOLAR ELECTRICAL CURRENT: CUTTING AND HEMOSTATIC ENERGY

The bipolar needle electrode is composed of two 5 cm long needles, in parallel, that connects to a bipolar energy source. By electric current, it dissects and cauterizes the tissue that lies between the needles. This technique facilitates the procedure, creating a regional ischemia, without hilar occlusion. It is very efficient to coagulate deep parenchymal vessels before cutting out the renal tissue. Its linear shape can be a limitation to different tumors locations.

Barret et al. compared the efficacy and morbidity between three hemostatic techniques: high-frequency bipolar, high-frequency unipolar, and ultrasound during LPN in a porcine model without vascular control. In this study, the authors evaluated perioperative complications, blood loss, renal function, and histological findings in the parenchyma. There was a significantly decrease in blood loss when the ultrasound was employed ($p = 0.0026$). One pig developed hemorrhage in day 6. There was no difference in histological results (28).

In another porcine study, Ong et al. demonstrated the use of the bipolar needle device in LPN with comparable results to those reported by Barret et al. (28). In this series, the blood loss was decreased (29).

Janetschek et al. and Guillonneau et al. reported the use of bipolar hemostatic coagulation in LPN showing the clinical feasibility of this energy to achieve good hemostasis (30,31).

Some modifications in the future, including curved shape or articulating head may expand the use of this device for midpole and hilar renal masses. It seems that the damage to the remaining tissue is minimal. Nevertheless, more clinical studies are required to define the proper role in LPN.

FLOATING BALL: CUTTING AND HEMOSTATIC ENERGY

The TissueLink Floating Ball (Tissuelink Medical, Inc., Dover, NH) comprises a monopolar

Table 2 – *Use of water jet during laparoscopic partial nephrectomy.*

Author/Year	Animal Model vs. Clinical	Acute vs. Chronic	Open vs. Laparoscopic	Hilar Clamp	Hemostatic Method
Pentchev (7), 1993	dog model	chronic	open	no	suture ligation
Hubert (8), 1996	porcine model	acute	open	no	suture ligation
Shekarriz (10), 2000	porcine model	acute	laparoscopic	yes	electrocautery
Corvin (9), 2001	porcine model	acute	laparoscopic	no	electrocautery Endo-GIA
Moinzadeh (25), 2005	calf	acute and chronic	laparoscopic	no	Biclamp
Penchev (11), 1999	clinical	human	open	no	suture ligation
Basting (12), 2000	clinical	human	open	no	suture ligation coagulation

*** Adapted from Moinzadeh et al.: Water jet assisted laparoscopic partial nephrectomy without hilar clamping in the calf model. J. Urol. 2005, 174: 317-21*

current that combines water-cooled with radio frequency for blunt dissection and coagulation purposes. The technology uses the radio frequency close to the instrument tip, sealing small blood vessels, achieving good hemostasis prior to parenchymal resection. The electrical energy is transmitted by the saline irrigation and converted into thermal energy on the target tissue. Scar formation is prevented by the saline since the coagulated area remains cool, maintaining the temperature at or bellow 100º C (32).

Sundaram et al. first reported the feasibility of LPN with the Floating Ball without vascular control in 3 patients (33). The mean estimated blood loss was 275 mL and one patient had a urine leak that resolved spontaneously. Urena et al. retrospectively reviewed 10 LPN where this energy source was used to achieve hemostasis. Mean tumor size was 3.9 cm and mean blood was 352 mL. All margins were negative (32).

Stern et al. reported the largest series available (34). The authors performed 14 LPN using the Floating Ball. The mean operative time in this series was 124 minutes and mean blood loss was 168 mL. The argon-beam coagulator, Fibrilar™ (Ethicon, Somerville, NJ) and fibrin glue were used for control minor bleeding.

The parenchymal resection is slower when performed without hilar control. To minimize the bleeding, the renal tissue can be coagulated prior to resection, and the scar produced does not affect the pathological analysis of tumor margin status. Vascular structures up to 3 mm can be sealed by the use of the floating ball device. The depth of tissue penetration is correlated to the type and duration of contact between the kidney surface and the device.

HARMONIC SCALPEL: CUTTING AND HEMOSTATIC ENERGY

The harmonic scalpel (LaparoSonic Coagulating Shears; Ethicon Endo-Surgery, Cincinati, OH) has the potential to vibrate its jaws at a rate of 55,000 Hz, generating heat in the range of 50º C TO 100º C, coagulating and cutting the tissue simultaneously. This device forms a protein coagulum between the jaws of the shear resulting in minimal spread of energy laterally (2 mm).

Jackman et al. showed the ability of the harmonic scalpel to perform LPN in a porcine model without control of the hilar vessels (35). Additional hemostatic measures were necessary in 25% of the cases when a polar nephrectomy was performed. The authors concluded that the use of harmonic scalpel in hemiphrectomies is not recommended because the high risk of substantial hemorrhage.

Harmon et al. reported the use of harmonic scalpel in 15 patients undergoing LPN (36). All procedures were completed without complications. The mean tumor size was 2.3 cm and mean blood loss was 368 mL. The renal bed hemostasis was accomplished by using oxidized cellulose and argon beam coagulator. All resection margins were negative at the pathology results.

Although this device may aid in dissection of small superficial renal tumors, it is not sufficient to perform LPN particularly for larger and centrally located tumors. Overall, the use of this technology has not shown good results when used without others hemostatic device/agents.

ELECTRICAL SNARE: CUTTING AND HEMOSTATIC ENERGY

This device was designed as a combination of an electrosurgical snare electrode (Cook Urological Inc., Spencer, IN) with an electrosurgical generator (ERBE USA, Inc., Marietta, GA), to produce renal transection and parenchymal hemostasis simultaneously.

Elashry et al. compared the effectiveness of this snare during LPN, comparing it to ultrasonic dissectors in the porcine model. The electrical snare was faster and produced less intraoperative bleeding than the ultrasonic dissectors (37).

In the study from Washington University reporting the use of the electrosurgical snare in LPN without occlusion of hilar vessels (38), the hemostasis was successfully achieved in all but one case, where it was necessary to use the argon-beam coagulator to stop the bleeding after parenchymal resection.

The limitations of this device include capability of using only for guillotine resections and it can not be safely used close the hilum because of risk

of renal pelvis injury. Clinical trials are still being awaited to confirm its applicability in LPN.

RADIO FREQUENCY ABLATION: TISSUE HEMOSTATIC - ABLATIVE ENERGY

The Radio Frequency Ablation (RFA) creates a good parenchymal zone of coagulative necrosis usually visible after 24 to 48 hours post procedure. This treated tissue is finally replaced by inflamation and fibrosis (39). In animal studies, Gill et al. demonstrated the renal parenchyma trombosis and coagulation noted after RF ablation (40,41).

The first clinical report on RFA assisted LPN was published by Gettman et al. (42). The RFA was used in 10 patients mainly to coagulate the tumor, facilitating the tumor excision with minimal bleeding. The Texas University group published the initial series of RFA assisted LPN (43) with 13 patients undergoing surgery. A total of 5 tumors were completely excised and 7 tumors were left in situ after treatment. There was one focal positive margin in a patient submitted to RFA assisted LPN, but this patient remained disease-free after 1 year treatment.

In these studies the authors reserved the use of this RFA technique for polar, small, exophytic lesions. There are some advantages related to complete tumor removal instead of only ablation, providing better oncologic approach for the patient. There is also minimal blood loss and good visualization during tumor excision. The limitations are concerned about the need for a learning curve with the RFA probes, the challenge to perform centrally located tumor excisions with high risk of collecting system injury. An additional clinical experience with larger diameter tumors and long-term follow-up is necessary to confirm the real value of this technique.

ARGOM-BEAM COAGULATOR: HEMOSTATIC ENERGY

The argon beam coagulator (ABC) provides hemostasis by delivering radiofrequency electrical energy to tissue across a jet of argon gas. The device uses a non-contact, monopolar, electrothermal type of hemostasis (44).

The first report using the ABC was from Daniell et al. when they reported its use in cholecystectomies in animals and humans. They concluded that the ABC allowed a safely hemostasis and effective controlled tissue electrocoagulation (45).

These techniques have been used associated to others kind of hemostatic agents, and with different approaches by another authors with relatively success (46-48).

The ABC allows a good visualization without smoke, safe hemostatic tissue electrocoagulation, with a rapid non-touching technique. The lack of smoke and the non-touching technique facilitate laparoscopic application. In the authors' opinion, this kind of energy is well used to coagulate cortex vessels after closing the parenchymal defect but has limited application for larger, infiltrating tumors. The use of the device must be done with caution because of the risk of gas embolism caused by intra-abdominal overpressurization during a laparoscopic procedure; to minimize the associated risks we must leave one instrument cannula open to drain the gas and have a good patient monitorization (e.g., end-tidal CO_2, Doppler flow).

CONCLUSIONS

LPN has emerged and gained popularity in selected centers worldwide, and new energy sources have been employed to minimize the level of difficulty of the procedure. The key to achieve an ideal procedure remains in simplify the technique as regards closure of collecting system and minimal blood loss without the need for hilar occlusion. The improved energy sources may further decrease operative time, warm ischemia time, and morbidity. The different devices presented are evolving but until today, no one has been totally superior and only the future will show us which of these instruments will stand the test of time.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Inderbir S. Gill
Section of Laparoscopic and Robotic Surgery
Glickman Urological Institute, A100
9500 Euclid Avenue
Cleveland, OH, 44195, USA
Fax: + 1 216 445 7031
E-mail: gilli@ccf.org

Review Article
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Epigenetic Targets in the Diagnosis and Treatment of Prostate Cancer

Murugesan Manoharan, Kavitha Ramachandran, Mark S. Soloway, Rakesh Singal

Department of Urology (MM, MSS) and Sylvester Comprehensive and Cancer Center (MM, KR, RS, MSS) Miller School of Medicine, University of Miami, Miami, Florida, USA, and Miami VA Medical Center (RS), Miami, Florida, USA

ABSTRACT

Prostate cancer (PC) is one of leading cause of cancer related deaths in men. Various aspects of cancer epigenetics are rapidly evolving and the role of 2 major epigenetic changes including DNA methylation and histone modifications in prostate cancer is being studied widely. The epigenetic changes are early event in the cancer development and are reversible. Novel epigenetic markers are being studied, which have the potential as sensitive diagnostic and prognostic marker. Variety of drugs targeting epigenetic changes are being studied, which can be effective individually or in combination with other conventional drugs in PC treatment. In this review, we discuss epigenetic changes associated with PC and their potential diagnostic and therapeutic applications including future areas of research.

Key words*: prostate cancer; DNA methylation; epigenesis, genetic*
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INTRODUCTION

Prostate cancer (PC) is one of leading cause of cancer related deaths in men. In the United States, an estimated 230,000 men were diagnosed with PC in the year 2005 and approximately 30,000 are expected to die from this cancer annually (1). Epigenetics refers to stable non inherited changes in the gene expression without alterations in DNA structure (2).

With the advent of prostate specific antigen (PSA) in 1998, there has been dramatic increase in the diagnosis of PC (3). The American Cancer Society recommends annual screening of men above the age of 50 for PC with PSA and rectal examination (4). However, it is not clear whether the PSA is effective in the diagnosis of PC as it lacks both specificity and sensitivity (5,6). About 25% men with normal PSA may harbor PC (5) and PSA less than 20 ng/mL may not differentiate between PC and benign conditions (6). This leads to unnecessary prostate biopsies and on the other hand, we might miss PC in patients with low PSA. Similarly, there is lack of effective prognostic markers to predict the behavior of PC and outcome following definitive treatment. Novel biomarkers based on epigenetic profiling are being explored to aid in the diagnosis and management of PC (7-9).

Epigenetics is one of the rapidly expanding fields in cancer related research. Recent studies have shown that epigenetics plays an important role in cancer biology, somatic gene therapy, viral infections, genomic imprinting. Epigenetic changes, particularly the DNA methylation is found to be involved in a

variety of cancers including colon, lung, breast and ovarian cancers apart from prostate cancer (8). Unlike passively transferred genetic mutations, the epigenetic changes must be actively maintained and its "reversibility" makes them a potential therapeutic target (10).

In this review, we discuss epigenetic changes associated with prostate cancer and their potential diagnostic and therapeutic applications including future areas of research.

BASICS OF EPIGENETICS

Genome

Approximately 23,000 genes are contained in the human genome. For proper functioning of the cells, these genes should be expressed in specific cells at specific times (11). The chromatin is a nucleoprotein complex made of nucleosomes. The nucleosomes are made of DNA, which are wrapped around octamers of globular histone proteins (12). The changes in the chromatin structure influence the gene expression. When the chromatin is condensed, the gene expression is "switched off" and when it is open, the gene expression is "switched on" (13). The status of chromatin is dynamic and can be controlled by reversible epigenetic mechanisms.

The two important, well studied epigenetic mechanisms are DNA methylation and histone modifications such as acetylation. These two processes can act independently and/ or together affecting the gene expression and in turn the tumorigenesis.

DNA Methylation in Prostate Cancer

DNA methylation refers to a covalent chemical modification, resulting in the addition of a methyl (CH3) group at the C-5 position of the Cytosine ring in the DNA. The human genome is not uniformly methylated. "CpG islands" are small regions within the genome that are rich in Cytosine and Guanine bases and are mostly unmethylated (8). Epigenetic alterations target this region thereby affecting gene expression. Both the hyper and hypomethylation can affect the gene expression and the role of DNA methylation in oncogenesis has been studied for several years.

DNA Hypermethylation

DNA hypermethylation is a well established epigenetic abnormality seen in several malignancies, more importantly in prostate cancer (9). Carcinogenesis is a multi step process and hypermethylation is hypothesized as an early event in the development and progression of prostate cancer (14). Hypermethylation of the gene is facilitated by a group of enzymes known as DNA methyltransferases (DNMT), which includes DNMT1, DNMT1b, DNMT1o, DNMT1p, DNMT2, DNMT3a, DNMT3b and DNMT3L (15). The hypermethylation involves the CpG islands in the promoter regions that results in the silencing of the genes that are involved in tumor suppressor activity, DNA repair and other critical cellular mechanisms.

Some of the important genes that are frequently hypermethylated in prostate cancer are listed in Table-1. Glutathione S-transferase P1 (GSTP1) is a protector gene and silencing this gene by hypermethylation leads to DNA damage and cancer initiation (7,16). Methyl Guanine DNA methyl transferase (MGMT) is another DNA repair gene which are silenced by hypermethylation (17). Inactivation of putative tumor suppressor genes by hypermethylation, such as Ras association domain family 1 gene (RASSF1A) (18,19), KAI 1 (20), Inhibin-alpha (21) and DAB21P (22). Hypermethylation promotes carcinogenesis in prostate cancer by affecting cell cycle control, hormonal response, cell adhesions and architecture (14).

Table 1 – *Hypermethylated genes in prostate cancer.*

Gene	Mechanism
GSTP1	DNA repair
RARB	Hormone response
CD44	Tumor invasion
RASSF1	Signal transduction
MGMT	DNA repair
AR	Hormone response
ESR1,2	Hormone response
APC	Tumor invasion
DAB21P	Signal transduction

DNA Hypomethylation

DNA hypomethylation is a second type of methylation related epigenetic aberration seen in variety of malignancies including prostate cancer (23). Hypomethylation is facilitated by enzyme group demethylases which includes 5-methylcytosine glycosylase and MBD2b (24). Methylation of normal genomes act as defensive mechanisms against cancer, for example, the oncogenes can be transcriptionally silenced and prevented from propogating by being methylated. The hypomethylation causes breakdown of this defense mechanism and is implicated in the tumor genesis.

The hypomethylation can be "global" or "localized". Global hypomethylation refers to overall decrease in methylation content in the genome. Bedford et al. reported that global hypomethylation is significantly lower in patients with metastatic prostate cancer compared to non metastatic prostate cancer (23). Localized or gene specific hypomethylation refers to a decrease in cytosine methylation relative to normal levels. This affects the specific regions within genome such as promoter regions of oncogenes which are highly methylated (9).

Histone Code

Histones have emerged as important regulators of chromatin, thereby controlling gene expression. In each nucleosome, two super helical turns of DNA containing around 146 base pairs wrap an octomer of histone core made of four histone partners (an H3-H4 tetramer and two H2A-H2B diamers (25). Histones consist of a globular domain and a more flexible and charged NH2 terminal called as histone "tail". These tails which are placed peripherally are susceptible for a variety of covalent modifications, such as acetylation, methylation, phosphorylation and ubiquitination. These modifications are referred as "the histone code" and is effective epigenetic mechanism regulating gene expression (26).

Histone acetylation and deacetylations are mediated by histone acetyl transferases (HAT) and histone deacetylases (HDAC) respectively. Huang et al. and Tsubaki et al. reported that treatment of prostate cancer cells with HDAC inhibitors results in increased expression of specific genes such as CPA3 (27) and Insulin like growth factor binding protein 3 (28). Coxsackie and adenovirus receptor (CAR) gene and Vitamin D receptor gene have been shown to be affected by histone acetylation in prostate cancer. Decreased CAR expression is associated with an increased Gleason score (29).

Histone methylation affects the chromatin function depending on the specific amino acid being modified and the extent of methylation (30). Methylation of H3 at lysine 4 is associated with inactive transcription of the PSA gene in prostate cancer cell line LNCaP and decreased di and trimethylated H3 at lysine 4 is associated with AR mediated transcription of the PSA gene (9). No histone demethylases have been described so far and it is postulated that histone methylation may be relatively stable and even irreversible (30).

DNA Methylation - Histone Code Interplay

DNA promoter methylation and histone deacetylation can act synergistically resulting in inactive chromatin state resulting in suppression of gene expression (Figure-1). Methylated DNA binding proteins such as MeCP2 may play an important role. Retinoic acid receptor beta gene (RARB) which is silenced in prostate cancer tissues and cell lines is regulated by both methylation and histone acetylation. This indicates that combined treatment targeting methylation and histone acetylation may result in reversal of epigenetic silencing of tumor suppressor genes (9,31). Similarly, DNA methylation and histone methylation may interact to facilitate chromatin silencing. However, it is unclear which event takes place first (9).

Epigenetic Diagnostic Markers

Prostate specific antigen (PSA) is a less than optimal tumor marker and cannot effectively differentiate between prostate cancer and other conditions such as prostatitis, benign prostatic hyperplasia. The false positive results lead to expensive and invasive investigations such as transrectal prostate biopsy. This provides the opportunity to the researchers to identify potential epigenetic markers in the diagnosis of prostate cancer.

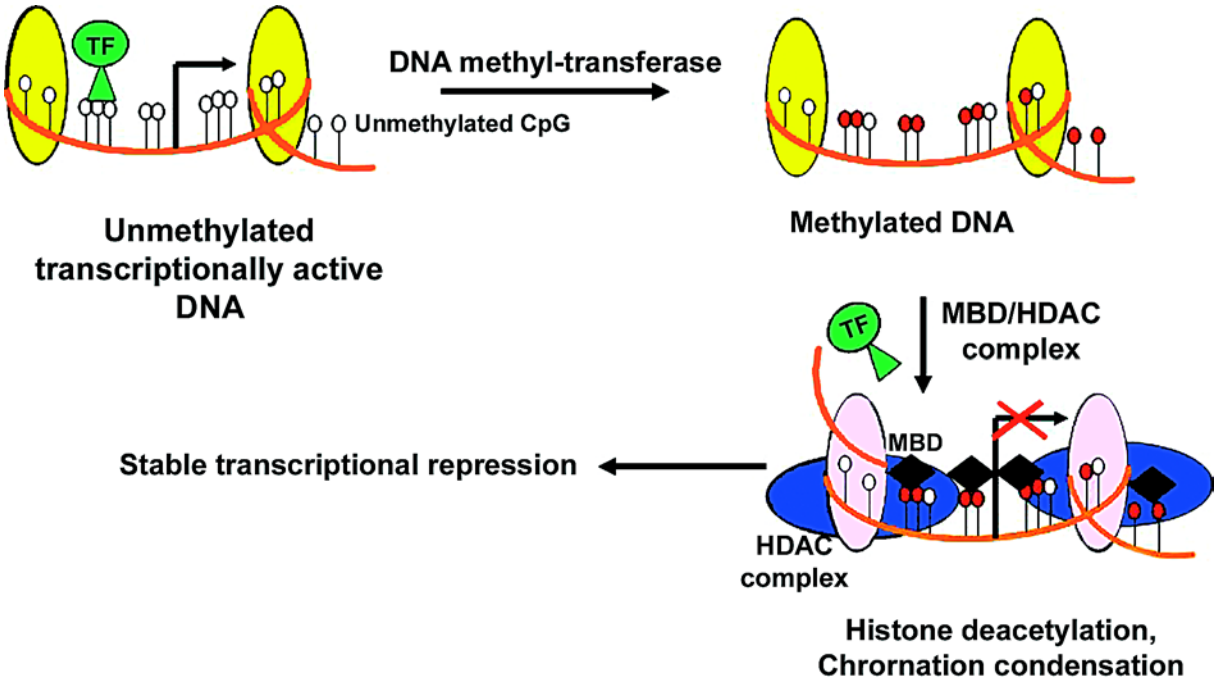

Figure 1 – *Epigenetic silencing of gene expression. DNA methyl-transferases carry out the methylation of CpG dinucleotides, which triggers the process of gene silencing by recruitment of methyl binding domain (MBD) and Histone deacetylases (HDAC) to bind to the methylated DNA. This results in histone deacetylation and chromatin condensation leading to loss of transcription factor binding and subsequent repression of transcription.*

Epigenetic markers, particularly aberrant DNA methylation, have the potential as an useful diagnostic tumor marker. These markers can be detected in cancer tissues, serum and body fluids. The methylation markers have several advantages over the mutation based genetic markers. The detection of these markers is technically simple and can be sensitively detected both quantitatively and qualitatively by polymerase chain reaction (PCR). Furthermore, the incidences of aberrant DNA methylation are higher than those of mutations are and can be discovered by genome wide screening procedures (32).

In the recent years, the role of GSTP1 is being studied as a tumor marker widely. Gossel et al. reported that GSTP1 hypermethylation is seen in the serum of 72% patients with of Prostate cancer patients (33). They also examined the urine after prostatic massage and methylation was detected in 68% patients with early prostate cancer and 78% of patients with locally advanced cancer. Table-2 shows methylation of GSTP1 in different tissue and body fluids. Harden et al. reported 73% GSTP1 methylation in prostate cancer tissue samples. They also reported that methylation assay with histological analysis improves the diagnostic specificity (34). Methylation of several other genes have been studied in the diagnosis of prostate cancer including, RARB, CD44, E- cadherin (ECAD), RASSF1A, APC and tazarotene induced gene 1 (T1G1) (7,35). Recent

Table 2 – *GSTP1 methylation in prostate cancer (8,33).*

Specimen	Methylation (%)
Tissue	90
Serum	72
Ejaculate	50
Urine after prostate massage	76

studies reported by Yegnasubramanian et al. (36) and others have reported that use of a panel of methylation markers including GSTP1 improves the diagnosis of prostate cancer both in body fluids and tissues. Further studies are needed before these markers can be used as diagnostic markers in the routine clinical practice.

Prognostic Markers

Kollerman et al. demonstrated that GSTP1 hypermethylation is seen in 40% of pre operative bone marrow aspirate in patients with advanced PC (37). They also found evidence of GSTP1 hypermethylation in 90% of PC patients with lymph node involvement where as in only 11% of lymph nodes in non cancer group. Genes such as CAV1, CDH1, CD 44 and T1G1 may exhibit specific methylation in high risk and Metastatic tumors that can be used in the molecular staging and predictors of disease progression (14). Prostate cancers with high Gleason score are correlated with a higher degree of methylation of many genes, such as RARβ, RASSF1A, GSTP1 and CDH13 (8). Further studies also indicate that use of panel of multiple methylation makers can be better predictors than individual genes (38).

THERAPEUTIC TARGETS

Epigenetic changes are heritable and potentially reversible. Hence, it is reasonable to expect that these can be used as potential therapeutic targets. Currently there are several drugs which are at different stages of development. They can be broadly classified in two groups: (i) DNMT inhibitors and (ii) Histone Deacetylase (HDAC) inhibitor. Some of the drugs in both groups, which are being tested and used currently, are shown in Table-3.

DNMT Inhibitors

5-aza-2' - Deoxycytidine (5-aza-dC) is one of the early drugs identified as DNMT inhibitor after being as cytotoxic drug around 1990. This drug forms irreversible covalent bonds with DNMT1 after its incorporation in to DNA, thereby inducing degradation of DNMT1 (39) Issa et al. (40) demonstrated that low dose continuous administration is more effective than higher doses. Myelosuppression is a known side effect of this drug which is otherwise well tolerated. 5-aza-dC has been recently approved by FDA for clinical use in certain hematological conditions. Another drug in the same group, Zebularine can be administered orally or intraperitoneally. It has to be given in high doses, however, it is chemically stable and has low toxicity (41). Other drugs in this which are being studied include Epigallocatechin-3 - Gallate (EGCG), Procainamide, Procaine and MG 98 (32).

Histone Deacetylases (HDAC) Inhibitors

A variety of natural products exhibit HDAC inhibitory activity. Commonly used HDAC inhibitors which are being tested include trichostatin A (TSA), Suberoylanilide hydroxamic acid (SAHA) and valproic acid (9). Many of these drugs have exhibited antitumor activity. SAHA and sodium butyrate have shown prostate cancer inhibition in animal models (42,43). Overall, low toxicity rates of these drugs are encouraging in conducting further studies.

Table 3 – *Drugs used for epigenetic modifications (9,32).*

DNMT Inhibitors	HDAC Inhibitors
5-aza-2'- Deoxycytidine	Trichostatin A (TSA)
Zebularine	Sodium butyrate
Procainamide	Suberoylanilide hydroxamic acid (SAHA)
Procaine	Valproic acid
Epigallocate chin-3-gallate (EGCG)	Pyroxamide
MG98	Phenyl butyrate

The combination of HDAC and DNMT inhibitors has synergistic effect in the reactivation of silenced gene (9). Another interesting possibility is the combination of epigenetic drugs and conventional anti androgens and chemotherapeutic agents. It should be cautioned that the epigenetic drugs currently lack gene specificity and some of them are associated with significant toxicity. Hence, efforts are being made to develop gene specific epigenetic drugs (32).

SUMMARY AND FUTURE DIRECTIONS

Epigenetic changes in prostate cancer are being studied extensively at present and genome wide screening will lead to development of novel epigenetic markers. Epigenetic changes are early event in cancer development and hence can be used to assess the risk of developing cancer. Li et al. suggest that genes such as CAV1, CDH1, CD44 and T1G1 should be explored further as "risk markers", particularly to differentiate the indolent tumors from others with bad prognostic potential (14). Epigenetic molecular classification will help to identify patients at high risk of recurrence following definitive treatments such as radical prostatectomy. Therapeutic drugs which reverse these epigenetic changes have the potential to be an effective adjunct treatment for prostate cancer. However, they need to be studied both for its efficacy and safety profile. Gene specific epigenetic drugs need to be developed for better targeting of the disease. As the epigenetic changes are early event in the PC development, these drugs have a potential to play a role in disease prevention. Two main features of epigenetic changes, "reversibility" and being an "early event" in tumorigenesis, makes epigenetic targeting as an important future research area for cancer diagnosis, risk stratification, treatment and prevention resulting in effective cancer control.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Murugesan Manoharan
Associate Professor of Urology
University of Miami School of Medicine
P.O. Box 016960 (M814)
Miami, Florida, 33101, USA
Fax: + 1 305 243-4653
E-mail: mmanoharan@med.miami.edu

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Percutaneous Nephrolithotomy with and without Retrograde Pyelography: A Randomized Clinical Trial

Ali Tabibi, Hamed Akhavizadegan, Kia Nouri-Mahdavi, Mohammad Najafi- Semnani, Mojgan Karbakhsh, Ali R. Niroomand

Section of Urology, Dr Labbafinejad Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Section of Urology, Baharloo Hospital (HA) and Department of Community Medicine (MK), School of Medicine, University of Tehran, Tehran, Iran

ABSTRACT

Objective: Since the introduction of percutaneous nephrolithotomy (PCNL), many changes have been added regarding the entrance to pyelocalyceal system such as insertion of the needle pointed to an opaque stone as a guided landmark. We aim at comparing the outcomes of managing renal calculi with and without retrograde pyelography.
Materials and Methods: In a randomized clinical trial, 55 cases with opaque renal calculi candidates for PCNL with stone in one calyce, in the pelvis or both in one calyce and the pelvis simultaneously were included in a nine-month study. They were randomized into 2 groups, noncatheterized (n = 28) and catheterized (n = 27), called intervention and control groups, respectively.
Results: The 2 groups had similar distributions regarding gender, age, duration of operation, length of hospital stay, past history of any surgical procedures on kidney, and stone size. Outcome (residual stone based on aforementioned management) was evaluated with plain X-ray on the morning following the operation. Postoperative hemoglobin decrease was significantly higher in controls than in the intervention group ($p < 0.001$) (with no clinical significance). No difference in outcome, postoperative fever, duration of surgery, duration of hospital stay and radiation exposure was observed between the 2 groups.
Conclusion: Our findings showed no differences in major clinical outcomes between the 2 groups (with and without catheter insertion for retrograde pyelography).

***Key words**: urolithiasis; percutaneous nephrolithotomy; pyelography*
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INTRODUCTION

Since the introduction of percutaneous nephrolithotomy(PCNL), many changes have been added regarding the entrance to pyelocalyceal system such as insertion of the needle pointed to an opaque stone as a guided landmark (1) (vs. the classic method of system enhancement with retrograde injection of air or contrast media) (2). Both methods have been widely used but we did not find any randomized clinical trial comparing them. In the classic method, the surgeon must perform an additional procedure to insert a ureteral catheter. Thus, if the latter is as efficient as the former in the elimination of stones, it is a good idea to perform PCNL without catheter insertion. In this study, we aim at comparing the clinical outcomes of renal calculi management with and without retrograde pyelography.

MATERIALS AND METHODS

In a randomized clinical trial, 55 cases with opaque renal calculi in one calyce, renal pelvis or one calyce and renal pelvis simultaneously who were candidate for PCNL were included in a 9 month study (from September 2003 to June 2004). All patients had intravenous pyelography without any anatomical abnormality before surgery. They were randomized into 2 groups without (n = 28) and with ureteral catheter insertion (n = 27) (called intervention and control groups, respectively). Age, gender, past history of any surgical procedures on kidneys, side of the involved kidney, postoperative hemoglobin decline, postoperative fever, duration of PCNL (in minutes), radiation duration, length of hospital stay and outcome (stone-free, insignificant residuals, need for extracorporeal shock wave lithotripsy, need for additional PCNL and need for transureteral lithotripsy were recorded for each patient. PCNL was performed classically in the controlled group, with the insertion of the ureteral catheter and the performance of a retrograde pyelography (with air or contrast media) and the assessment to the proper calyce.

In the intervention group, the pyelocalyceal system was approached with the insertion of a small needle toward the opaque stone, without any ureteral catheter insertion. In fact, after viewing the stone with fluoroscopy, the needle is inserted toward it. In case it is proved to be successful for the system, entrance (i.e. urine aspiration) the contrast media (urographin) is injected to find out if the direction of the needle in the system is appropriate (a blood-less route like calyceal caps or fornices). If so, dilatation is performed. Otherwise, a better direction is tried using the enhanced system toward the stone. On the other hand, if the first trial for the system entrance was not successful, the second puncture is performed under the guide of fluoroscopy targeting the stone. Enhancement of the system with intravenous pyelography is used only if multiple attempts for the system entrance were not successful. After dilatation, lithotripsy was performed with lithoclast (ballistic source).

Postoperative outcome was evaluated using plain X-ray performed on the morning after procedure.

SPSS version 10 was used for statistical analysis. Kolmogrov-Smirnov test was used to test for normality of quantitative variables. Student t test and non-parametric (Mann-Whitney U) test were used for statistical analysis. $P \leq 0.05$ was considered as significant.

RESULTS

The 2 groups had similar distributions regarding gender, age, past history of any surgical procedures on kidneys except for the side of kidney stone. Demographic features and other characteristics of the two groups are demonstrated in Table-1. There was no significant difference between the 2 groups

Table 1 – *Demographic characteristics of the 2 studied groups.*

Characteristic	Group		p Value
	Control (with retrograde pyelography)	Intervention (without retrograde pyelography)	
Gender (% male)	77.78 (21 patients)	64.28 (18 patients)	0.27
Age (mean ± SD)	43.81 ± 13.78	45.93 ± 13.14	0.56
History of any surgical procedure on kidneys	96.15% (25 patients, one missing)	85.71 (24 patients)	0.186
Side of the involved kidney (% right)	77.8 (21 patients)	48.1 (13 patients) (one missing)	0.027*
Stone size (mean of 2 diameters)	3.2 ± 0.7	2.9 ± 0.5	0.7

* *Significant*

regarding stone location (calyce, pelvis, or calyce and pelvis simultaneously). The findings of the major outcomes are presented below.

Mean duration of surgery was 73.2 ± 26.37 minutes in catheterized group and 62.86 ± 17.66 in the noncatheterized group ($p > 0.05$).

The average duration of radiation exposure in the noncatheterized group was 2.58 ± 1.47 and 2.66 ± 1.2 minutes in the other ($p > 0.05$).

Hospital stay in the catheterized group was 2.7 ± 1.08 and 2.93 ± 2.16 days in the noncatheterized group ($p > 0.05$).

Prevalence of post-PCNL fever in catheterized was 23.2% versus 18.5% in the noncatheterized group ($p > 0.05$).

Postoperative hemoglobin decrease was significantly higher in PCNL in the catheterized (2.29 ± 1.25) when compared to the noncatheterized group (1.03±0.9) ($p < 0.001$).

No difference in outcome was observed between the 2 groups ($p = 0.136$). Around 93 percent of the patients in the catheterized group ($n = 26$), were stone free on the day after operation, whereas in the noncatheterized group, only 78.6 percent of the patients ($n = 22$) were stone free on the day after operation. One patient in the noncatheterized group and 5 patients in the catheterized group needed ESWL. Additional PCNL was required in one patient in the noncatheterized group. Even after recoding outcome (stone free vs. else) no difference was detected between the 2 groups ($p = 0.2$).

COMMENTS

To this date, experience with PCNL without catheter has been limited to catheter insertion preoperatively and removing immediately afterwards (3). In this research, the catheter was not inserted from the beginning in the intervention group and the outcomes were compared with the classic PCNL.

In the classical approach to pyelocalyceal system, the system is opacified with retrograde pyelography with air or contrast media (2). Using a catheter may facilitate access to enhanced system (due to some pyelocalyceal distension) and can provide us with better directions in PCNL (4); though we did not find such benefit. In PCNL with catheter, a constant access to pelvis is provided and in case of any complications, successful management is more achievable.

Access to enhanced system may theoretically reduce blood loss (5,6) (due to entrance via a hypovascular plane) and decrease the incidence of residual stones (due to most proper direction), but we did not find such benefits. It seems that targeting the stone from a point medial to the posterior axillary line (maximum 4-finger width lateral to the para-vertebral muscle), saves this hypovascular plane. Entrance to the system with antegrade pyelography has been widely used (1) and fluoroscopic evaluation of the collecting system during antegrade pyelography is probably the best technique to use (7) but in normal systems with simple stones, like what we had in our cases, performing retrograde pyelography does not sound necessary. In addition, the enhanced system may need less radiation exposure or reduce the total time of surgery; though no difference was observed in this regard.

Using balloon ureteral catheter insertion in PCNL has some benefits such as inhibiting migration of stone particles to the ureter (4). Due to financial implications, it is not a routine to use balloon ureteral catheter for PCNL in our center and simple ureteral catheter is used instead. Nevertheless, migrated ureteral stones are infrequently seen in our cases. In our study, the rate of migrated ureteral stones needing ureteroscopy was not different in the 2 studied groups. This finding is also justifiable, as simple ureteral catheter used in the control group does not provide any protection in this regard as discussed above.

The use of ureteral catheter may introduce bacteria from the lower urinary tract to the upper system and its insertion requires another procedure (cystoscopy) to the patients. In addition to this potential complication, air embolism may rarely occur during retrograde pyelography (8). In this study, no increase in the rate of post-PCNL fever was observed in PCNL either with a catheter or without it. Moreover, PCNL without ureteral catheter can reduce postoperative discomfort due to less pain and less

urine leakage, although this was not assessed in our study.

CONCLUSION

No differences in major clinical outcomes were observed between PCNL either with or without catheter. Considering other benefits of PCNL without stent insertion (e.g. no need to cystoscopy and lower amount of urine leakage as only one catheter is inserted in the urethra), it is a safe alternative procedure. Selection of patients for PCNL without catheter may be limited to those with opaque stones in pelvis or/and in one calyce. It is also a safe procedure for accessing to pyelocalyceal system in patients with difficulty for cystoscopy (due to positioning or urethral stricture).

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Hamed Akhavizadegan
Shahid Dr. Labbafinegad Hospital
9th Boostan Street, Pasdaran Avenue
Tehran, Iran
E-mail: hamed_akhavizadegan@yahoo.com

EDITORIAL COMMENT

It is long known that the urinary system may be enhanced by injecting contrast media through a ureteral catheter or directly by a lumbar needle puncture. Such enhancement may ease the establishment of the nephrostomy tract. The choice of the calyx to be punctured, preferentially through a posterior calyceal papilla, is based on the stone size and location, and also on the morphology of urinary tract. Generally the calyx chosen for puncture must offer the best nephroscope access to calyces with stones and to renal pelvis.

In a selected group of patients, the authors clearly demonstrated that percutaneous surgery might be performed with the same efficacy using or not a ureteral catheter. Such conclusion does not necessarily imply in a change of conduct, but reinforces that the ureteral catheter is not an indispensable tool for percutaneous surgery, especially in patients where it is impossible to insert it.

The insertion of a ureteral catheter is a 10 minutes procedure that allows the injection of contrast media, saline or air, and may be useful to prevent migration of stone fragments to the ureter (not observed in this paper). It may also allow the introduction of a guide wire during the percutaneous surgery for a double J catheter insertion whenever it is needed.

The great merit of this paper is showing that percutaneous surgery may be successfully accomplished without the insertion of a catheter. Nevertheless, the suggestion of abolishing such procedure is unwise, as it has the aforementioned advantages. The surgeon will never regret inserting the ureteral catheter, but may regret not doing so.

Dr. Anuar I. Mitre
Associate Professor of Urology
Sao Paulo University Medical School
Sao Paulo, SP, Brazil
E-mail: anuar@mitre.com.br

EDITORIAL COMMENT

The authors of this manuscript have challenged the long-held dogma, that retrograde ureteral catheter insertion and contrast administration is necessary for safe and successful percutaneous renal access prior to percutaneous nephrolithotomy (PCNL). Many of us who perform PCNL have likely been faced with the situation where retrograde opacification of the collecting system was impossible due to previous urinary diversion or ureteral obstruction. In those instances, the use of intravenous contrast or antegrade pyelography to allow collecting system opacification, or the use of ultrasound to guide renal access are alternatives.

In this paper the authors conducted a small randomized trial to compare the outcomes between a group of patients undergoing PCNL in the conventional way utilizing retrograde ureteral catheter insertion versus a cohort in which percutaneous access was achieved without the use of a retrograde catheter. Exactly how patients were randomized is not detailed in the paper; however it is confirmed that the 2 groups were similar preoperatively with respect to age, sex, previous kidney surgery and stone size. Whether stone location was similar between groups is not mentioned. This would seem to be an important piece of information because if I understand their technique correctly, needle insertion is performed directly onto the stone when retrograde contrast was not used, regardless of whether the stone was calyceal or renal pelvic in location.

The risks with blind insertion into a stone-bearing calyx are likely less than the potential problems with placement of the needle directly into the renal pelvis. Although direct needle access into the renal pelvis is unlikely to cause much harm in most patients, potential vascular concerns must be acknowledged. Once urine is obtained, antegrade contrast is injected to delineate the collecting system. With direct renal pelvic needle placement and if contrast extravasation occurs, one must wonder if this may impede fluoroscopic visualization, and make proper tract access more difficult. The authors indicate that should access not be achievable without the use of retrograde contrast they will resort to intravenous contrast. How often this was required in their series is not documented.

In the presentation of the results, it is mentioned that the duration of surgery, radiation time and hospital stay was not different statistically between the 2 groups. Blood loss was higher in the catheterized group, with no explanation provided to account for this. The authors claim the stone free rates were not different statistically either, however a review of the raw data would suggest otherwise: They report 26 patients in the catheterized group were stone free. With a denominator of 27 this would equal a 96.3% stone free rate, not the 93% rate mentioned in the paper. In the non-catheterized group they report 22/28 (78.6%) stone free rate. As such I would argue the differences are in fact more significant than they have claimed.

In the discussion section, the authors list the potential advantages associated with the avoidance of ureteral catheter insertion. Although it is always healthy to be critical of traditional doctrine, the arguments supporting a change of current practice must be compelling. The authors claim that a separate procedure is required to perform retrograde catheter insertion. At our centre as at many others, flexible cystoscopy and catheter insertion with the patient prone is performed immediately prior to and as a part of the PCNL procedure. The risk of air embolus with retrograde air injection is an extremely rare event if the volume of air used is small. Finally, postoperative patient discomfort from the ureteral catheter is highlighted, but in the majority of instances the ureteral catheter can be removed at the conclusion of the PCNL procedure before the patient is even awakened from anesthesia. In my mind the arguments presented do not seem compelling enough to warrant a modification in technique in my own practice.

Having said that though, the authors have given us food for thought and should be commended for their efforts to further refine PCNL. As I read this paper I recalled the words of one of my earliest endourology mentors, who used to say, “percutaneous nephrolithotomy is a procedure of millimeters”. To paraphrase, he was trying to say that surgical precision is important in to the safety and success of this operation. As such whatever technical modifications we consider must preserve that tenet.

Dr. Hassan A. Razvi
Chair, Division of Urology
University of Western Ontario
London, Ontario, Canada
E-mail: hrazvi@uwo.ca

REPLY BY AUTHORS

I read the editorial comments. I agree with the items that are suggested in comments. The less invasive method must be the safer method. This way is only an alternative to classic method in special cases.

We think that only entrance of needle to vessels does not cause any problem. Moving the needle through that direction (from behind near tip of 12th rib to stone) very rarely may encounter the renal pelvis directly.

In this study no patient need IV administration of contrast media.

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Comparison of the Clinical and Pathologic Staging in Patients Undergoing Radical Cystectomy for Bladder Cancer

Sean McLaughlin, Jon Shephard, Eric Wallen, Susan Maygarden, Culley C. Carson, Raj S. Pruthi

Division of Urologic Surgery, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

ABSTRACT

Purpose: Radical cystectomy (RCx) is perhaps the most effective therapeutic approach for patients with muscle-invasive bladder cancer. Unfortunately, clinical staging is imprecise and the degree of understaging remains high. This study retrospectively evaluated patients undergoing RCx with regard to pathologic outcomes and degree of upstaging to better identify features that may lessen clinical understaging.
Materials and Methods: 141 consecutive patients with urothelial bladder carcinoma who were candidates for RCx with curative intent were retrospectively evaluated. Preoperative clinical and pathological (i.e. TURBT) features were compared to pathological outcomes in the cystectomy specimen. Patients were also evaluated as to whether cystectomy was performed as their primary (n = 91) versus secondary (n = 50) treatment for recurrent/progressive disease. Date of cystectomy (≤ 5 years vs. > 5 years prior to study) was also analyzed.
Results: Of the 141 patients, 54% were upstaged on operative pathology. The greatest degree of upstaging occurred in those with invasive disease preoperatively (cT2-T3). Twenty-six percent of all patients had node-positive disease, and 75% of cT3 patients were node-positive. Seven of 101 (7%) patients with clinical T2 disease were unresectable at the time of surgery. In the primary (vs. secondary) RCx group, more patients were upstaged (63% vs. 40%), non-organ confined (62% vs. 38%), and LN positive (31% vs. 20%). In the more modern cohort, the degree of upstaging was not improved.
Conclusions: Pathologic findings after RCx often do not correlate with preoperative staging. Over half of patients undergoing cystectomy are upstaged on their operative pathology. An improved understanding of the relative frequency of upstaging in cystectomy patients may have important implications in the decision-making and selection for neoadjuvant and adjuvant therapies for these high-risk populations.

Key words: *bladder cancer; neoplasm staging; cystectomy; pathology*
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INTRODUCTION

After prostate cancer, bladder cancer is the most common urologic and the fifth most common overall malignancy.

In 2005, there were approximately 63,000 new cases of bladder cancer diagnosed and over 13,000 disease-related deaths in the United States (1). The majority of new bladder tumors are superficial (60 - 75%) and of those, up to 20% can be expected to progress to muscle invasive disease (2). Nevertheless, a significant number of muscle-invasive tumors are diagnosed at initial presentation in patients with no prior history of TCCa.

The most common therapeutic approach for invasive bladder cancer is radical cystectomy. Recent improvements in surgical technique and perioperative management have reduced complication rates and operative mortality for this procedure (3,4). Despite the improvements in surgical morbidity, up to 50% of patients undergoing cystectomy will experience local or distant recurrence. Unfortunately, most of these patients who are destined to recur are not easily distinguished upon pre-operative evaluation. Such findings highlight the significant clinical under-staging that occurs in bladder cancer patients undergoing cystectomy. Our inability to prospectively identify non-organ-confined disease or systemic micrometastases remains a shortcoming of current preoperative evaluation. Consequently, many patients are upstaged at the time of surgical exploration and extirpation.

This retrospective review sought to characterize patients who are upstaged at the time of cystectomy in order to better identify pre-operative factors, which may contribute to more aggressive/ advanced disease. Factors including cross-sectional imaging (and improvements that may have occurred in recent years), impact of bladder-sparing therapies (i.e. those undergoing a primary versus secondary cystectomy), as well as other clinical and demographic factors were also evaluated.

MATERIALS AND METHODS

We retrospectively examined the medical records of 141 consecutive patients with urothelial cancer of the bladder that underwent radical cystectomy (RCx) for clinically-localized disease and with curative intent from 1990 to 2002. Age, race, gender, tumor grade, clinical stage, pathological stage information for each patient were extracted.

Patients were also analyzed as to whether RCx was performed as primary therapy after their initial diagnosis (primary cystectomy or PRCx) (n = 91), or whether RCx was performed for recurrent or progressive disease after bladder-sparing treatments were first utilized (secondary cystectomy or SRCx) (n = 50). Of note, PRCx patients had no prior history of intravesical therapies and received no neoadjuvant treatment modalities (e.g. chemotherapy or radiation therapy). In the SRCx group, all patients had received bladder-sparing regimens after their initial diagnosis including intravesical BCG immunotherapy (n = 41), intravesical chemotherapy (n = 8), partial cystectomy (n = 3), radiation therapy (n = 2), or a combination of these modalities.

In addition, comparisons were made with regard to date of cystectomy (before 1997, n = 54 vs. 1997-2002, n = 87) in order to evaluate for possible improvements in clinical staging that may have occurred in the most recent 5 years (e.g. improvements in resolution of cross-sectional imaging).

All cystectomy specimens were received fresh in pathology, opened anteriorly, pinned open and fixed overnight in 10% buffered formalin. The next day, the external aspect of the bladder was inked, and margin sections were taken of the ureters and urethral margins. Standard bladder sections were taken to include 3-4 samples of any grossly visible tumor to include the areas of deepest gross invasion, sections of any mucosal abnormality, and random sections of the dome, anterior, posterior, right lateral and left lateral wall, and trigone. Sections of any attached organs were taken if present. In male patients, two sections of each lobe of the prostate and one section from right and left seminal vesicles were taken as initial sampling, with additional sections submitted if significant findings were present on these initial sections. One section of each submitted lymph node was taken. All sections were routinely processed, paraffin embedded, and stained with hematoxylin and eosin.

The nonparametric Jonkheere-Terpstra method was used to test for ordered differences among categories. With this test, the null hypothesis is that the distribution of the response does not differ across ordered categories. The nonparametric Wilcoxon signed-rank test was used on calculated pair difference values. All p values were adjusted using the Bonferroni method to account for multiple testing or comparisons. Statistical analyses were performed with SAS statistical software, Version 8.2, SAS Institute Inc., Cary, NC.

RESULTS

The clinical characteristics of the patient cohort are shown in Table-1. Of note, there were no differences in age, gender composition, or racial composition between those upstaged versus those who were not. It should be noted that only 4 patients (2.8%) were classified as low grade or grade-1: all others were classified as high grade or grade-2 or 3. Since the vast majority were classified as moderate or high grade, grade was not therefore not a useful distinguishing or predictive characteristic with regarding to upstaging of disease.

Of 141 patients, 54% were upstaged at pathologic staging. The degree of upstaging stratified by clinical stage is shown in Table-2. The greatest degree of upstaging occurred in those with invasive disease pre-operatively (cT2-T3). Of note, 26% of all patients were ultimately proven to have node-positive disease, and 75% of those with clinical T3 disease were node-positive. In addition, 7 of the 101 (7%) patients with clinical T2 disease were found to be unresectable at the time of surgery (bulky adenopathy, significant local extension/fixation). Those undergoing PRCx were upstaged to a greater degree (63% vs. 40%) for the entire cohort and at each level of clinical stage.

Table-3 shows the clinical stage, and Table-4 demonstrates the pathological staging of the entire cohort. Tables-3 and 4 also stratifies these results based on patients undergoing PRCx vs. SRCx. The median time between diagnosis and cystectomy was significantly different between the PRCx group (2 months; 0-6 months) vs. the SRCx group (22 months; 5 - 149 months). Whereas most patients in the PRCx group were clinical T2 or higher (87%), those patients undergoing SRCx were less often clinical T2 or greater (58%). This difference also was observed upon comparisons of pathological staging as well. More patients were upstaged (63% vs. 40%), non-organ confined (62% vs. 38%), and lymph node positive (31% vs. 20%) in the PRCx versus SRCx group.

The vast majority of all patients underwent CT imaging (11%) with the remainder of patients undergoing MRI (89%). When patients were stratified into those staged ≤ 5 years versus > 5 years, a greater percentage of patients underwent CT imaging before 1997 (93%) than in the most recent time period (87%). When patients were stratified into those staged ≤ 5 years versus > 5 years there were no significant differences between these time periods with regard to upstaging. (Table-2 and Figure-1).

Table 1 – *Patient characteristics.*

Patient Cohort	**N = 141**
Mean Age (range)	66 years (32-86 years)
Gender	
Male	100 (71%)
Female	41 (29%)
Race	
Caucasian	122 (87%)
African American	16 (11%)
Other	3 (2%)

Table 2 – *Clinical stage and degree of upstaging.*

Clinical Stage	**% Upstaged: All patients**	**% Upstaged PRCx**	**% Upstaged SRCx**	**% Upstaged > 5 years**	**% Upstaged ≤ 5 years**	**% Nodal Disease**
Ta,Tis,T1 (n = 33)	30	42*	24	28	33	0
T2 (n = 101)	62	68*	52	54	60	40
T3 (n = 4)	100	100	100	100	100	75
T4 (n = 3)	0	0	0	0	0	33

**p < 0.05 vs. SRCx*

Table 3 – *Clinical stage of patients undergoing cystectomy.*

Clinical Stage	All	Primary RCx	Secondary RCx
≤ T1 (n = 33)	23%	13%*	42%
T2 (n = 101)	72%	81%*	54%
T3 (n = 7)	5%	6%	4%

**p < 0.05 vs. SRCx*

Table 4 – *Pathologic stage of patients undergoing cystectomy.*

Clinical Stage	All	Primary RCx	Secondary RCx
≤ T1 (n = 38)	27%	19%*	42%
T2 (n = 29)	21%	20%*	20%
T3/4 (n = 37)	26%	25%	18%
N+ (n = 36)	26%	31%	20%

**p < 0.05 vs. SRCx*

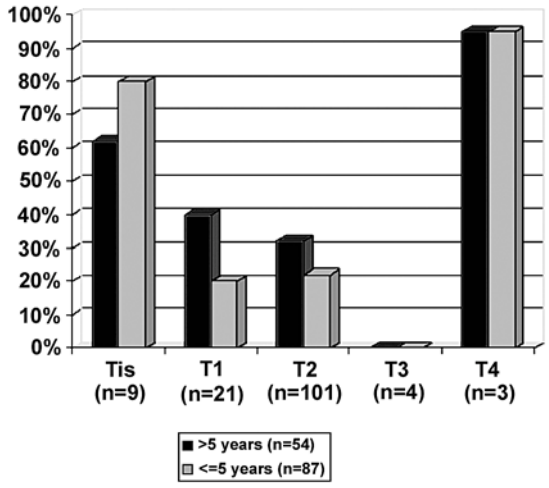

Figure 1 – *Percentage of patients upstaged stratified by clinical stage and date performed.*

COMMENTS

It is clear that patients with clinically-localized disease are not necessarily a uniform population with varying outcomes with regard to operative pathology and, accordingly, disease-free survival (DFS). For example, of patients with clinically-localized disease, those with organ-confined disease (pT0-pT2, N0) on surgical pathology have 5-year DFS rates exceeding 70%, while those who are found to have non-organ-confined disease (pT3-4, N+) have rates of less than 30%. Our inability to prospectively identify non-organ-confined disease remains a shortcoming of current pre-operative evaluation. Consequently, many patients (over half in the present series) are upstaged at the time of surgical exploration and extirpation. To this end, several investigators have sought to identify strategies to better identify and stage such patients pre- and intra-operatively including the use of molecular and immunohistochemical markers (e.g. p53), novel imaging techniques (e.g. photon emission computed tomography/CT (SPECT/CT) and ferumoxtran-10-enhanced MR imaging), and directed (e.g. sentinel node detection) or extended lymph node dissection (5-9).

Nevertheless, several reasons may account for this large degree of surgical upstaging, including delay between diagnosis (i.e. TURBT) and cystectomy. Recent studies have suggested that such a delay is associated with worse pathological findings at the time of cystectomy. Chang et al. have shown that delaying definitive surgery more than 90 days confers a worse pathologic stage with significantly more non-organ-confined disease (2). Similarly, Sanchez-Ortiz et al. have also demonstrated that when cystectomy is delayed greater than 12 weeks, patients had higher pathological stage and overall decreased survival (3). This time period varies from patient to patient as some seek additional opinions, pursue neoadjuvant therapies, or are completing a metastatic evaluation and clinical staging. Nevertheless, such delays may worsen pathological and survival outcomes, and attempts should be made to avoid such a delay.

This study sought to identify whether patients who were delayed from undergoing their radical

cystectomy due to prior bladder-sparing therapies (SRCx) had a higher risk of understaging than those who underwent radical cystectomy as their initial mode of treatment (PRCx). In other words, do initial bladder sparing interventions (e.g. intravesical therapies) contribute to increased surgical upstaging and worse pathological outcomes as compared those who undergo immediate cystectomy? Interestingly, this was not the case. In fact, those undergoing PRCx actually faired worse in the both clinical and pathologic findings and were understaged to a lesser degree, especially in clinical stage T2 and T3 disease. However, the belief that SRCx patients fare better than PRCx patients is almost certainly attributable to a selection bias. Patients in the SRCx group were likely more favorable candidates from the outset: the decision to utilize bladder-spring therapies are likely due to, in part, more favorable clinical and pathological features. Indeed, this group had a higher percentage of T1 (and CIS) tumors at the initial staging.

Thus, one should not extrapolate that patients will fare better if there is a delay in definitive therapy with regard to radical cystectomy, particularly with invasive disease. It merely suggests that selected patients may be appropriate candidates for bladder-sparing modalities and should not necessarily expect a worse pathologic staging if conservative measures fail and they progress to cystectomy. Still, despite the more favorable outcomes with regard to pathological staging seen in the SRCx group, 40% of these patients were ultimately understaged and 38% had pT3/T4 or node-positive disease at the time of cystectomy. That is, those who receive delay in treatment may still be subject to relatively high incidence of upstaging and extravesical disease on operative pathology. Such findings suggest that some patients in this group would fare better with earlier cystectomy.

In addition to the potential role of delay in upstaging of patients undergoing cystectomy, limitations in the clinical staging of invasive bladder cancer may also lead to surgical upstaging by failing to recognize non-organ confined disease at the time of diagnosis. The lack of an appropriate and reliable serum, urine, or other molecular marker for bladder cancer forces reliance on standard methodology for clinical staging. Thorough endoscopic resection of all visible tumors (with an appropriate sampling of muscle), bimanual exam, and cross-sectional imaging provide clues in determining the clinical course of bladder cancer. For large volume disease, current CT and MRI can be reliable in determination of clinical stage. Subtle invasive disease or tumors with low volume or small nodes are less accurately staged with these imaging modalities, however. Accordingly, multiple studies have shown disappointing correlation between clinical and pathologic stages using existing axial imaging. Specifically, computed tomography (CT) has been shown to have limited accuracy in correlating clinical to pathologic stages. Paik demonstrated CT accuracy to be around 55% with understaging at 39% (10). Barentsz et al. reported CT accuracy ranged from 40 to 92% but MRI had up to a 30% accuracy improvement over CT (11). Low volume lymph node disease is found in a third of invasive disease, and is it difficult to discern on CT or MRI. Herr reported two-thirds of patients in a series with node positive disease were understaged (12). Indeed, our data demonstrates that over half of patients are upstaged on operative pathology, and 7% of clinical T2 patients are found to be unresectable at the time of surgery. Ultimately, CT lacks the ability to reliably detect small volume extravesical disease or demonstrate lymph node metastases. Some have speculated that positron emission tomography (PET) may be useful in prospectively distinguishing localized tumors from regional or distant disease, but recent studies have demonstrated that current PET imaging is at best two-thirds reliable in staging node-positive bladder cancer disease and is still an expensive modality not found at many tertiary centers (13-15).

Even with improved resolution of more recent CT or MRI scanners, better outcomes with regard to clinical staging does not seem to follow. This was evident across the time span of our retrospective review. Despite marked advances in our radiographic modalities, which are integral to clinical staging, we saw no difference in the stage discrepancy in patients who were staged more than 5 years ago compared to those within the past 5 years (Figure-1).

An important limitation of our study is the retrospective nature of this analysis. Such an analysis does not allow for quantification of the degree of upstaging based upon suboptimal transurethral resection or nor does it stratify patients who underwent multiple TUR procedures. Bayrakatar and colleagues published a series that demonstrated substantial overstaging in TUR, which led to premature radical surgery (16). However, Dalbagni et al. showed understaging at the time of cystectomy was negligible in T1 disease after performing a restaging TUR procedures (17). Still, the many differing TUR techniques employed by the referring urologists in this study contribute to added variability of clinical staging.

In addition, a retrospective analysis does not account for the impact of selection bias on those undergoing PRCx versus SRCx, and makes interpretation of those results inherently imperfect (see discussion above). Nevertheless, this report reflects the patient population observed at a tertiary care facility at which the referral population is often varied especially with regard to decision-making for and selection of prior therapies.

Lastly, a large part of this analysis was based clinical and pathologic staging without regard to tumor grade. However, only 4 patients (< 3%) were low grade or grade-1 in this series. In other words, the cystectomy population was almost uniformly high grade, which thereby makes the predictive ability of tumor grade, with regard to upstaging, unattainable.

CONCLUSION

Pathologic findings after definitive radical cystectomy for urothelial carcinoma of the bladder does not often correlate with preoperative staging. Consequently, more than half of patients undergoing cystectomy will be upstaged on their operative pathology. Patients who undergo secondary RCx (for recurrent/progressive disease after initial bladder-sparing modalities) have more favorable pathology at the time of cystectomy and are understaged to a lesser degree than patients who receive a primary radical cystectomy. However, these findings may be tempered by a selection bias that is likely found in this subgroup. Still, a significant number of these patients undergoing SRCx will be understaged and found to have extravesical disease at the time of cystectomy. An improved understanding of the relative frequency of upstaging in cystectomy patients may have important implications on the decision and selection for neoadjuvant and adjuvant therapies for these high-risk populations.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Raj S. Pruthi
Division of Urologic Surgery
The University of North Carolina at Chapel Hill
2140 Bioinformatics Bldg, CB7235
Chapel Hill, North Carolina 27599, USA
E-mail: rpruthi@med.unc.edu

EDITORIAL COMMENT

In this retrospective study, authors demonstrate the difficulties in accurate preoperative clinical staging in patients undergoing radical cystectomy (RC). This study highlights several important issues. Firstly, there are no reliable diagnostic tools available to accurately stage bladder cancer (BC). There is an urgent need to develop accurate imaging studies and markers to stage the disease accurately and predict the prognosis. Secondly, this study demonstrates that more than 50% of patients undergoing RC are under staged and perhaps unfairly denied neoadjuvant chemotherapy. This may support the argument that all patients with ≥ T2 bladder cancer may benefit from neoadjuvant chemotherapy (1).

Timing of RC in patients with CIS and T1 high grade bladder cancer is controversial (2). Accurate staging of patients undergoing intravesical BCG therapy and in those who failed BCG therapy is important as studies have demonstrated disease progression to higher stage (> T2) in patients undergoing RC (3,4).

Until accurate imaging studies and markers are available, thorough bimanual examination during transurethral resection remains an important staging tool. As authors suggested patients should be formally counseled regarding potential under staging preoperatively.

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Dr. M. Manoharan
Director, Bladder Cancer & Neobladder Center
Miller School of Medicine
University of Miami
Miami, Florida, USA
E-mail: mmanoharan@med.miami.edu

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Stereological Study of Collagen and Elastic System in the Detrusor Muscle of Bladders from Controls and Patients with Infravesical Obstruction

Mauricio Rubinstein, Francisco J. Sampaio, Waldemar S. Costa

Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil

ABSTRACT

Objective: Compare detrusor muscle of normal and patients with infravesical obstruction, quantifying the collagen and elastic system fibers.
Materials and Methods: We studied samples taken from bladders of 10 patients whose ages ranged from 45 to 75 years (mean = 60 years), 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).
Results: The results of collagen and elastic fibers quantification (volumetric density) demonstrated the following results in percentage (mean +/- standard deviation): collagen in BPH patients = 4.89 +/- 2.64 and 2.32 +/- 1.25 in controls ($p < 0.0001$), elastin in BPH patients = 10.63% +/- 2.00 and 8.94% +/- 1.19 in controls ($p < 0.0001$).
Conclusion: 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.

Key words*: bladder, prostatic hyperplasia, bladder outlet obstruction, collagen, elastin*
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INTRODUCTION

The benign prostatic hyperplasia (BPH) is a pathologic process that contributes but is not the only cause of lower urinary tract symptoms in men. It is recognized today that part of the symptoms in men with BPH may be the result of a detrusor muscle dysfunction related to age (1).

In patients with bladder outlet obstruction (BOO), in addition to hypertrophic changes in smooth musculature, other changes related to the collagen and to the elastic system fibers were already evidenced. However, most of theses studies were conducted on animals (2-4).

Kondo & Susset (2) did not verify changes in collagen in bladders of dogs subjected to infravesical obstruction. On the other hand, an increase in the amount of collagen was described by Dixon et al. (4) in bladders of swine subjected to partial urethral obstruction.

Uvelius & Mattiasson (3) described in rats, the decrease in the amount of collagen in detrusor muscle hypertrophy caused by infravesical obstruction.

Nielsen et al (5) subjected 9 pigs to chronic partial infravesical obstruction through an urethral ring. The results showed an 8-fold increase in total collagen and in type I and III collagen.

Collagen and elastic fibers are the main components of extracellular matrix; they are present in the bladder wall and are closely related to vesical compliance (6). The increase of collagen and other components of extracellular matrix occur as a tissue response to injury and can lead to fibrosis of the organ. Previous studies have demonstrated that collagen synthesis is increased in pulmonary fibrosis (7), in glomerulosclerosis (8) and in other pathologies.

Congenital or acquired infravesical obstruction can result in a fibrotic vesical wall, characterized by trabeculation, increase of connective tissue, low volumetric capacity under high pressures and, in some cases, the occurrence of non-inhibited contraction of detrusor muscle. The vesical wall can accumulate connective tissue and evolve to a fibrotic process in consequence of a neurologic (myelomeningocele, spinal cord lesion) or obstructive (BPH) process. Such pathological conditions can result in low capacity, high pressure and low vesical compliance (9).

This study aims to compare bladders of normal patients and those with infravesical obstruction, quantifying by stereological and computer-assisted methods the collagen and elastic system fibers of detrusor muscle.

MATERIALS AND METHODS

We studied samples with approximately 2 x 2 cm, including all the layers of vesical dome, taken from bladders of 10 patients whose ages ranged from 45 to 75 years (mean = 60 years), who underwent transvesical prostatectomy for treatment of BPH. The prostatic mass removed weighted 95 ± 10 grams in average. Previously to surgery, all patients were subjected to an urodynamic study in order to confirm and characterize the presence of BOO. A detrusor pressure above 100 cm of H_2O and an urinary flow lower than 10 ml/s were considered as urodynamic evidence of BOO. The methodology and definitions used in the work complied with the International Continence Society standards (10). All patients who presented vesical instability on the urodynamic examination were excluded from the study. In all cases an informed consent was obtained with the patient for removal of vesical samples.

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). The autopsy was performed up to 6 hours after death, and it was verified that there was no compromise of urogenital system organs. The removed fragments included all layers of vesical dome and measured about 2 x 2 cm. The study protocol was approved by the Committee on Human Research of the State University of Rio de Janeiro.

Immediately after the removal, the material was fixed in buffered formalin 10% (pH = 7.2) during 48 to 72 hours, and subsequently underwent a routine histological processing for inclusion in paraffin. The resultant blocks were then subjected to serial sections of 5-µm thickness, obtaining 10 sections from each bladder fragment.

Sections were stained by Picro-Sirius Red technique for evidencing collagen and by Weigert's Fuchsin-Resorcin for characterizing the elastic system fibers.

Image acquisition and analysis - Five sections were randomly analyzed, from each bladder, and in each section, 5 fields were analyzed, totaling 15 fields per bladder.

Quantification of the elastic system was made with sections stained by Weigert's Fuchsin-Resorcin. The analyzed fields were digitized to a final magnification of x400 using a video camera coupled to a light microscope. The alleatory histological areas were quantified using a M-42 test-grid system on the digitized fields on the screen of a color monitor. The stereological method has been described in detail elsewhere (11,12).

For quantification of collagen fibers the sections stained by Picro-Sirius Red technique were observed under polarized light (13). The analyzed images were obtained with a magnification of x400 using a video camera coupled to a light microscope.

The stereological parameter employed for estimating the contents of extracellular matrix (collagen and elastic system fibers) was volumetric density (Vv). Mean values of Vv were calculated for

both groups in relation to elastic fibers and collagen and subsequently compared.

Data were analyzed on Graphpad InStat software (Graphpad). Mann-Whitney test was used for analysis of results, considering a value of $p < 0.05$ as significant.

RESULTS

The observation of histological sections showed an increase of collagen and elastic system fibers in the detrusor muscle of patients with infravesical obstruction, compared to the controls (Figure-1).

The results of quantification of collagen and elastic system fibers are presented on Table-1.

DISCUSSION

The morphology of normal human bladder has been studied and compared to the obstructed bladder and to the elderly bladder through optic and

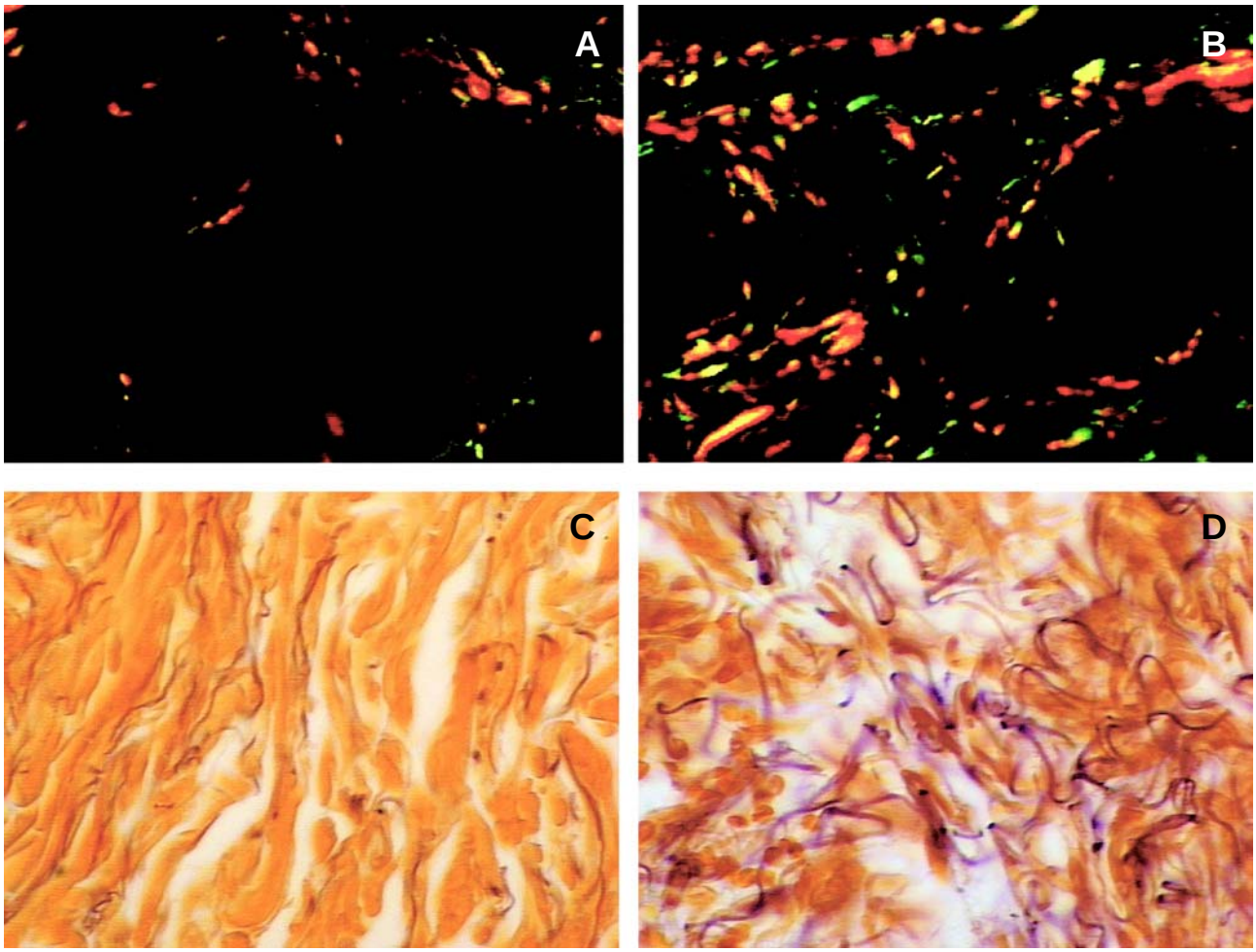

Figure 1 – *Picro-Sirius-Red staining under polarization microscopy of the bladder wall demonstrating the amount of collagen in controls (A) and patients with bladder outlet obstruction (B), X400. Weigert's Resorcin-Fucsin staining of the bladder demonstrating the amount of elastic system fibers in controls (C) and patients with bladder outlet obstruction (D), X400.*

Table 1 – *The volumetric density in percentage of collagen and elastic system fibers in the bladder of controls (n = 10) and benign prostate hyperplasia (BPH) samples (n = 10).*

	Collagen		Elastic System Fibers	
	Controls	**BPH**	**Controls**	**BPH**
Mean	2.32	4.89	8.94	10.63
Standard deviation	1.25	2.64	1.19	2.00
Standard error	0.39	0.83	0.37	0.63
Minimum	0.73	1.96	7.14	8.25
Maximum	4.31	8.27	10.63	14.12
P value	< 0.0001		< 0.0001	

electronic microscopy (6,14). In the bladder of patients without urologic disease, muscle fibers are grouped with few connective tissue between their bundles. In the obstructed bladder, however, many muscle fibers are surrounded by connective tissue bundles, and they also change their function, becoming involved in collagen synthesis (15).

Kim et al (16) analyzed in rats the effects of partial obstruction of bladder over type I and III collagen, and the relationship between detrusor contractility and types of collagen. The results showed an increase in total collagen following infravesical obstruction and a decrease following the obstruction's relief. This work suggests that a change in localization and quantity of collagen leads to vesical alterations, which can impair detrusor contractility. In our work, conducted in humans and employing a different methodology, confirms the findings by Kim et al. (16), demonstrating a significant increase not only in collagen but also of elastic system fibers in patients with vesical obstruction.

Cortivo et al. (6) evaluated the connective tissue of bladders of normal patients and patients with infravesical obstruction. Three distinct groups were assessed: 1) 3-month children with infravesical obstruction, 2) children between 4 to 8 years with partial infravesical obstruction and 3) adults with chronic infravesical obstruction. An increase of elastic tissue occurred in newborns and in adults with obstruction. Collagen did not present any changes between the groups under study. In this work, according to the authors, collagen and elastic fibers were not quantified. In our current study an important increase of elastic tissue was observed, corroborating, partially, the results from Cortivo et al. (6), however, differently from their work (6), our results demonstrated a significant increase of collagen in the detrusor muscle of patients with obstructive BPH.

Gosling & Dixon (17) compared microscopic findings from biopsies of the detrusor muscle with the grade of vesical trabeculation assessed by cystoscopy. The author observed an important infiltration of connective tissue elements in the detrusor muscle of patients with severely trabeculated bladders. Data from our current work, also show that collagen surrounds and infiltrates the muscle bundles, suggesting that fibrous elements can lead to a reduction of compliance in bladders of patients with infravesical obstruction.

Gilpin et al. (9) while studying the morphology and morphometry of detrusor muscle fibers from patients with obstruction, described structural changes of the vesical wall, represented by collagen deposit in muscular interstice, and by the increase in volume of muscle fibers, what is in accordance to our results.

Freedman et al. (18) demonstrated that the relationship between smooth muscle versus connective tissue remained the same in control (normal) and obstructed fetal bladders. These findings show that the amount of collagen associated with infravesical obstruction is also a controversial subject in human bladders.

Lepor et al. (19), with the purpose of characterizing the effects of aging and of obstructive

BPH over the vesical wall, conducted a retrospective study in 86 vesical samples, obtained from medical files, and removed during autopsies. The study was divided into 4 groups: 1) men aged between 35 and 45 years; 2) men aged between 65 and 75 years; 3) women aged between 35 and 45 years; and 4) women aged between 65 and 75 years. The groups were divided in order to select men with BPH and without BPH. There was a significant increase of density in the smooth muscle and connective tissue area in group 1 vs. group 2 (2.90 +/- 0.22 vs. 2.33 +/- 0.16) and in group 3 vs. group 4 (2.85 +/- 0.13 vs. 2.03 +/- 0.20). The increase in the connective tissue ratio was age-dependent in both female and male groups. Based on these results, the authors suggest that aging, and not BPH, is related to an increase of fibrosis in the detrusor muscle. Nevertheless, one must take into account that the examined material in this study came from patients who did not undergo urodynamic tests, that would confirm or not the presence of infravesical obstruction. In our study, the previous conduction of an urodynamic assessment confirmed the existence of an obstructive process in all the patients under study. Our results showed that there was a significant increase of collagen and elastic fibers when the groups of men with BPH and without BPH were compared.

The study by Holm et al. (20) questions if the fibrosis of the detrusor muscle is a consequence of infravesical obstruction, of the patient's age, or both factors. Morphological studies of vesical wall were performed through biopsies from young patients without disease, patients with infravesical obstruction, and elderly without obstruction. It was observed fibrosis inside and around the muscle fascicles, in the same proportion in obstructed patients and in elderly. The results from this work pose the question whether the fibrotic changes of detrusor muscle occur due to obstruction itself, to aging, or both.

Gosling (15) demonstrated that in the elderly, the bladder differs from the obstructed bladder regarding the collagen deposit. In the elderly bladder there is no evidence of collagen synthesis by smooth muscle fibers. On the other hand, in the bladder that is obstructed by BPH there is an accumulation of connective tissue in the detrusor muscle, where several smooth muscle fibers change their function, and become more involved with the collagen synthesis. Thus, the author concluded that it is unlikely that the changes occurring in the bladder of patients with obstruction merely reflect alteration due to aging. The results of the current work ratify these data (15), objectively demonstrating that, in the bladder obstructed by BPH, there is an accumulation of connective tissue in the detrusor muscle.

Deveaud et al. (21) analyzed 45 children who underwent surgical treatment for non-compliant and fibrotic bladders due to a number of causes (myelomeningocele, posterior urethral valve, vesicoureteral reflux). Vesical fragments were analyzed through immunohistochemical for localizing collagen. A major infiltration of connective tissue was evidenced in detrusor's smooth muscle bundles. The results showed an increase in total collagen, through dosing of total hydroxyproline content, and a significant increase in type I and III collagen. The work suggests that the collagen deposit in the detrusor muscle is a marked histological characteristic of non-compliant bladders, regardless of their etiology. Our results show a concordance with this work (21) even though the methodology and groups under study were different. In our study, even though a separate quantification of type I and type III collagen was not performed, the greenish color present in the sections observed under polarization microscopy is highly expressive and suggests the presence of a significant amount of type III collagen.

It is important to highlight that the majority of previous studies, in humans, were conducted without confirmation of an obstructive condition by urodynamic tests.

Inui et al. (22) observed changes in connective tissue of the detrusor muscle of patients with obstructive BPH. Thirteen normal men with ages ranging from 25 to 90 years (68.5 +/- 18) and 26 cases of BPH patients with ages between 60 and 94 years (71.6 +/- 9.2) were studied. BPH diagnosis was made based on the prostate transrectal ultrasonography. The mean values for connective tissue and smooth muscle between control and BPH cases were subsequently compared through computer assisted color image analysis. The authors found that abnormal increase of connective tissue in addition to smooth muscle

hypertrophy and/or hyperplasia could contribute to advanced bladder hypertrophy caused by infravesical obstruction. Our findings confirm the increase of connective tissue in patients with BPH and demonstrate a significant difference in the percentage of collagen and elastic system fibers between the control and BPH groups.

Recently, Collado et al. (23) studied by computer assisted morphometry the 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. The author found morphometric differences in detrusor muscle cell diameter and the connective tissue-to-smooth muscle ratio between controls and patients with obstruction. Also, it was found an increase in detrusor muscle cell diameter and fibrosis in bladder outlet obstruction, which are in agreement with our findings concerning extracellular matrix components.

The understanding of changes consequent to a response to vesical injury, may allow the development of strategies to prevent the pathologic remodeling of extracellular matrix observed in diseased bladders. Obstructive processes, diseases related to age, or even aging itself, can influence vesical function. The relationship between obstruction and aging has not been completely clarified. The lower urinary tract symptoms are not specific, and alone they do not enable the diagnosis of obstruction. The symptomatology in certain conditions, such as vesical instability and detrusor hypocontractility without obstruction, mimic those of obstructive BPH, but there is no proof that such conditions result solely from aging.

Even if we know that some changes occurring in the bladder that is subjected to infravesical obstruction are possibly related to aging processes, a comparison with bladders of normal young individuals, such as the one we performed on this work, can be useful for establishing a pattern of the different vesical components, which will be modified either by aging or by pathologic processes.

In conclusion, we found that the components of connective tissue, collagen and elastic system fibers are increased in the detrusor muscle of patients with infravesical obstruction.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
Waldemar S. Costa
Urogenital Research Unit - UERJ
Av. 28 de Setembro, 87 – fundos – FCM – terreo
20551-030, Rio de Janeiro, RJ, Brazil
Fax: + 55 21 2587-6121
E-mail: wscosta@gmail.com

EDITORIAL COMMENT

Bladder outlet obstruction produces histological changes in the detrusor, including an increased collagen concentration in adult and fetal bladders (1-4). The authors of this paper have corroborated that the components of connective tissue are increased in the detrusor muscle of patients with infravesical obstruction. While this is not the first study regarding the association between bladder wall

collagen deposition and bladder outlet obstruction, it is one of the first report to demonstrate a clear demarcation in collagen content and elastic systems fiber of the obstructed and unobstructed adult human male bladder. This study may enable us to better understand the human bladder reaction to bladder outlet obstruction. Studies of this type should be encouraged.

However, much more work needs to be done to establish a link between lower urinary tract symptoms and this histological finding. First, although they stated that the greenish color present in the sections observed under polarization microscopy suggests the presence of a significant amount of type III collagen, a separate quantification of type I and type III collagen was not performed and no analysis of collagen content by symptom type was reported. Second, no mention was made of compliance measurements. This is of potential since patients with a low compliant bladder expect to have a significant increase in connective tissue compared to those without a low compliant bladder (5). It would have certainly been useful to determine what level of bladder wall collagen is associated with detectable changes in bladder compliance. This work would add to the growing body of evidence linking specific changes in detrusor structure or function with lower urinary tract symptoms. Finally, the increase in the connective tissue may be age-dependent (4). Thus, it would be better to include elderly patients without bladder outlet obstruction in the study.

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Dr. Jae-Seung Paick
Department of Urology
Seoul National University Hospital
Seoul, Korea
E-mail: jspaick@snu.ac.kr

EDITORIAL COMMENT

In our urological practice, it is commonly found that patients with profound bladder outlet obstruction (BOO) may have a low bladder compliance. The low compliant bladder contributes to a high intravesical pressure and endangers upper urinary tract function. Moreover, in the patients with low bladder compliance, the detrusor contractility is usually inadequate to completely empty the bladder during micturition. The increased connective tissue density in the bladder wall may not only constrict the distensibility of the urinary bladder but also result in low bladder contractility.

In this article, the authors found the collagen and elastic system fibers increase in the bladder wall in the patients with urodynamically proven BOO compared to the bladders in the non obstructed cadavers. Previous studies have shown in patients with BOO and ageing, the collagen content

increases. The results of this study are compatible with the previous works using rat models and human bladders and further demonstrate that the connective tissue components are increased in the bladder wall of BOO in a group of patients with a mean age of 60 years.

Bladder "fibrosis" results in trabeculation, reduced capacity, increased intravesical pressure and suppressed detrusor contractility. This pathological change of the bladder wall is commonly found in varying diseases including neurogenic bladder, BOO, ageing and chronic cystitis. The true mechanisms for the increased connective tissue density in the bladder wall have not been completely elucidated yet. Recent studies have shown that BOO may induce increase in nerve growth factor (NGF) production in the suburothelium, which might result in a cascade of inflammatory reactions, lowering sensory threshold and remodeling of the micturition pathways (1). The increased NGF levels in bladder afferent pathways could contribute to the emergence of bladder overactivity as well as somal hypertrophy and hyperexcitability of bladder afferent neurons (2). It is interesting to find that in patients with transient BOO, the bladder compliance will turn to normal after relief of obstruction, however, in patients with chronic BOO, the changes of the bladder wall will not. Neural plasticity induced increase of connective tissue density in the bladder wall after BOO and the factors responsible for their reversibility deserve further investigations.

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Dr. Hann-Chorng Kuo
Dept. Urology, Buddhist Tzu Chi General Hospital
Buddhist Tzu Chi University
Hualien, Taiwan
E-mail:hck@tzuchi.com.tw

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Antibiotic Resistance and Trend of Urinary Pathogens in General Outpatients from a Major Urban City

Carlos R. Kiffer, Caio Mendes, Carmen P. Oplustil, Jorge L. Sampaio

Section of Microbiology, Fleury Institute, Sao Paulo, SP, Brazil

ABSTRACT

Objective: We assessed the antimicrobial resistance patterns of pathogens responsible for urinary tract infections (UTI) in outpatients in São Paulo, Brazil, as well as the Escherichia coli antimicrobial resistance trend.
Materials and Methods: Outpatients urine cultures were collected from January 2000 to December 2003. Statistical analysis considered positive results for one bacterial species with colony count ≥ 100,000 CFU/mL. Stratification was done on age group and gender. Statistical tests used included chi-square and the chi-square test for trend to evaluate differences between susceptibility rates among age groups and ordering in the E. coli resistance rates per year, respectively.
Results: There were 37,261 positive results with Enterobacteriaceae isolated in 32,530 (87.3%) and Gram-positive cocci in 2,570 (6.9%) cultures. E. coli had the highest prevalence (71.6%). Susceptibility tests were performed in 31,716 cultures. E. coli had elevated resistance rates (> 30%) to ampicillin, trimethoprim-sulfamethoxazole, and tetracycline. Significant differences between age groups and ordering among years were observed.
Conclusions: The use of trimethoprim-sulfamethoxazole is precluded in the population studied due to elevated resistance rates (> 30%) among most prevalent pathogens. Significant resistance rate differences among age groups and years were observed, particularly for fluoroquinolones. Fluoroquinolones should be used with caution. Nitrofurantoin should be used as empirical therapy for primary, non-complicated urinary tract infections.

Key words*: urinary tract infections; drug therapy; drug resistance; Escherichia coli*
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INTRODUCTION

Controlling the increase in antimicrobial resistance is a major issue confronting organized health care today. Although multiple factors play a role in this problem, the selective pressures of inappropriate and widespread use of antibiotics are considered major contributors. A few studies have analyzed the antimicrobial resistance patterns of bacteria causing community acquired urinary tract infections (UTI) (1-5). International resistance surveillance studies have shown an increasing resistance pattern against commonly used community antimicrobials (1-6). Surveillance programs may be valuable tools and may offer important information on bacterial resistance trends either per geographical location or per disease type in community or hospital settings (7,8). However, surveillance programs must be stratified by region and population, not to incur in general and mostly non-applicable conclusions. Regional studies analyzing community acquired UTI and their antimicrobial resistance pattern are currently needed in many areas, particularly major urban centers worldwide because of their specificities on antimicrobial usage density.

Thus, the goal of this study was to assess the most frequent pathogens responsible for urinary tract infections (UTI) in outpatients and their antimicrobial resistance pattern in São Paulo, Brazil, through consecutive urine samples collected during a four-year period, from January 2000 to December 2003. Additionally, the study also aimed at identifying possible resistance trends.

MATERIALS AND METHODS

From January 2000 to December 2003, routine urine cultures were consecutively collected at a private medical diagnostic center from patients residing in the São Paulo city area, Brazil. The city is located in Southeast Brazil and has around 10,000,000 inhabitants. The private medical diagnostic center has 12 collection sites distributed over the city area and serves mostly the population with access to private health care system within this area. All cultures were collected from outpatients with medical requests through midstream urine samples, except for children below 2 years old, who had collections by sterile collector vials. More than one culture from the same patient was only included in the database if collected more than 30 days apart.

Urine samples were plated on cystine-lactose-electrolyte-deficient (CLED), MacConkey and citrate agars (deep slide methodology) up to 20 minutes after collection and then incubated at 37ºC for 18 to 24 hours. Negative urine samples (refrigerated aliquot) after initial 24 hours incubation with abnormal leukocyte count (≥ 30,000/mL) or bacteriuria on direct non-centrifuged urine microscopic examination were also cultivated on blood agar and incubated for an additional 24 hours.

Identification of all isolates was done by VITEK (bioMérieux Inc., Durham, North Carolina, USA) automated system. Susceptibility testing was performed according to medical requests and was done by VITEK (bioMérieux, Inc.) automated system for Enterobacteriaceae and disk diffusion test (Oxoid, Basingstoke, Hampshire, UK) were used for Gram-positive bacteria and Pseudomonas aeruginosa. The following antimicrobials were tested against Gram-negative isolates: ampicillin, ceftriaxone, cephalothin, ciprofloxacin, gentamicin, nalidixic acid, nitrofurantoin, norfloxacin, tetracycline, and trimethoprim-sulfamethoxazole. The following antimicrobials were tested against Gram-positive isolates: ciprofloxacin, clindamycin, erythromycin, nitrofurantoin, oxacillin, penicillin G, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin (results not fully shown). Interpretative criteria used were for the respective years CLSI (formerly NCCLS) documents (9-12).

Only positive results with one bacterial species and a colony count ≥ 100,000 CFU/mL were considered for descriptive and inferential analysis. Stratification by gender and age was done, and age groups were divided as following: < 4 years-old; ≥ 4 and < 13 years-old; ≥ 13 and < 60 years-old; and ≥ 60 years-old. In order to investigate possible factors associated to resistance, E. coli, as the most prevalent microorganism, and its susceptibility rates to ampicillin, ciprofloxacin, nitrofurantoin, norfloxacin, tetracycline, and trimethoprim-sulfamethoxazole were defined as the dependent variables. Age groups were defined as the independent variables. The chi-square test was used to identify differences between the observed E. coli susceptibility rates of the six antimicrobials among all four age groups. Additionally, the Fisher exact test was used to evaluate differences between the observed resistance rates between < 13 and ≥ 60 years old groups (13). An exact 2-tailed P value was computed, as well as the confidence intervals around the differences using the normal approximation. Finally, the chi-square test for trend, as described by Altman 1991 (13), was applied to compare ordering between E. coli resistance rates to ampicillin, ciprofloxacin, nitrofurantoin, norfloxacin, tetracycline, trimethoprim-sulfamethoxazole, and nalidixic acid among the four years (2000 to 2003). P values below 0.05 were considered significant for all tests.

RESULTS

Frequency of Microorganism Isolation

There were 37,261 positive results and Enterobacteriaceae were isolated in 32,530 (87.3%) cul-

tures, followed by Gram-positive cocci with 2,570 (6.9%). E. coli presented the highest prevalence (71.6%), followed by Klebsiella pneumoniae (6.4%), Proteus mirabilis (6.1%), and Enterococcus faecalis (4.8%), Pseudomonas aeruginosa (1.8%), Staphylococcus saprophyticus (1.6%), Enterobacter aerogenes (1.6%), Enterobacter cloacae (1.1%), and others (5.0%).

Among the positive cultures, 88.8% belonged to female and 11.2% to male patients. Among the 33,090 UTI in females, 59.2% was detected in the population of ≥ 13 and < 60 years old. On the other hand, among the 4,171 UTI in males, 54.2% was detected in the population of ≥ 60 years old. The age group of < 4 years old contributed with 13.0% of cases in the male and with 4.4% in the female population.

Table-1 shows the total amount of microorganisms isolated per age group and gender. Overall, E. coli was the most prevalent isolate in all groups. K. pneumoniae, although with a significant prevalence, was more commonly isolated in the population ≥ 13 years old. P. mirabilis was more prevalent in the population ≥ 13 years old, although the population < 4 years old also presented a significant prevalence.

Susceptibility Patterns

Susceptibility tests were performed in 31,716 cultures. The susceptibility pattern of the most prevalent microorganisms isolated from UTI in outpatients is described in Table-2. E. coli presented resistance rate to ampicillin of 43.4%, followed by 33.7% to trimethoprim-sulfamethoxazole and by 30.5% to tetracycline. Ceftriaxone was the most active agent against E. coli (99.7% susceptible), with an extremely low resistance rate (0.3%). Also, E. coli presented low resistance rates to gentamicin and nitrofurantoin (3.0% and 2.9%, respectively). For K. pneumoniae, the second highest prevalent pathogen, significant resistance rates were noted to nitrofurantoin, tetracycline, trimethoprim-sulfamethoxazole and nalidixic acid (21.2%, 19.8%, 17.7%, and 15.2% respectively), with low resistance rates to ceftriaxone, gentamicin, and ciprofloxacin (1.7%, 3.3% and 6.0%, respectively). For P. mirabilis, the third most frequently isolated, considerable rates were observed only to trimethoprim-sulfamethoxazole and ampicillin (21.5% and 18.9%), apart from the intrinsic resistances to nitrofurantoin and tetracycline.

Statistics

E. coli was the most frequently isolated pathogen in all age groups (22,693) and the majority had susceptibility tests performed (22,679). Table-3 shows E. coli resistance rates to ampicillin, ciprofloxacin, nitrofurantoin, norfloxacin, tetracycline, trimethoprim-sulfamethoxazole and the chi-square

Table 1 – *Total amount of microorganisms isolated from UTI in outpatients and their distribution according to age groups and gender, years 2000 to 2003, São Paulo, Brazil.*

		Age Group							
		< 4 y-o		≥ 4 < 13 y-o		≥ 13 < 60 y-o		≥ 60 y-o	
Microorganism	**Total**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**
E. coli	26,693	972	252	1172	77	15230	730	7329	931
K. pneumoniae	2,391	75	24	76	6	1128	61	912	109
P. mirabilis	2,266	308	183	226	111	829	28	476	105
E. faecalis	1,803	14	6	55	8	665	82	649	324
P. aeruginosa	672	20	23	10	9	35	50	234	291
S. saprophyticus	606	0	1	6	2	566	7	20	4
E. aerogenes	596	10	15	7	0	375	21	131	37
E. cloacae	391	13	14	13	2	98	30	136	85
C. freundii	193	8	5	1	0	24	4	109	42
S. epidermidis	161	0	1	6	1	58	12	38	45

Table 2 – *Resistance pattern (%) of the most prevalent microorganisms isolated from UTI in outpatients, years 2000 to 2003, São Paulo, Brazil.*

Microorganism	Total	AMP	CFL	CRO	CIP	GEN	NAL	NIT	NOR	SXT	TET
E. coli	22,679	43.4	13.9	0.3	11.9	3.0	15.5	2.9	12.0	33.7	30.5
K. pneumoniae	2,059	100.0	7.6	1.7	6.0	3.3	15.2	21.2	8.9	17.7	19.8
P. mirabilis	1,944	18.9	3.1	0.4	4.2	2.3	8.9	100.0	4.0	21.5	100.0
E. faecalis	1,525	0.3	—	—	16.1	—	—	0.8	—	—	59.2
P. aeruginosa	605	—	—	89.1	63.4	48.3	—	—	61.6	—	—
S. saprophyticus	531	—	—	—	1.3	—	—	0.6	—	7.0	15.8
E. aerogenes	510	100.0	100.0	2.0	5.1	2.2	9.6	21.2	5.5	7.8	6.9
E. cloacae	331	100.0	100.0	32.9	38.7	24.2	44.4	39.6	41.1	38.4	47.0
C. freundii	168	100.0	100.0	20.2	22.6	12.5	28.6	8.3	21.4	25.6	53.5

— = Not tested; AMP = ampicillin; CFL = cephalotin; CRO = ceftriaxone; CIP = ciprofloxacin; GEN = gentamicin; NAL = nalidixic acid; NIT = nitrofurantoin; NOR = norfloxacin; SXT = trimethoprim-sulfamethoxazole; TET = tetracycline.

test with P values for comparisons of proportions among age groups.

Table-4 shows a test intended to identify possible ordered resistance rates of the most prevalent microorganism during the study period. The chi-square test for trend was performed for comparisons of the ordered differences between E. coli resistance rates to the described antimicrobials among the four years surveyed, i.e. 2000 to 2003.

COMMENTS

Uncomplicated UTI are amongst the most common infections in outpatient women with significant morbidity and health costs (14). This study did not discriminate among uncomplicated and complicated UTI in the sample evaluated and this could lead to a case mix with confounding variables in terms of resistance patterns. However, it should be noted that the vast majority of the samples collected from adults correspond to clean-catch midstream urine and that it is a common practice in our area to order urine cultures for uncomplicated UTI, since results are available no later than 48 hours after sample collection. Additionally, as stated, only one urine sample per patient in a 30-day period was entered in the database, diminishing the possibility of frequent UTI recurrences.

Although the spectrum of agents causing UTI in outpatients is relatively constant, their susceptibility patterns are different in different environments.

Table 3 – *Chi-square test for comparisons of E. coli resistance rates (%) to various antimicrobials among age groups.*

		E. coli Resistance Rate (%)					
Age Group	N	Ampicillin	Ciprofloxacin	Nitrofurantoin	Norfloxacin	Trimeth-sulfa	Tetracycline
< 4	969	60.8	0.9	1.9	1	49.6	33.7
≥ 4 and < 13	979	57.4	1.5	1	2.1	49.0	32.2
≥ 13 and < 60	13,675	39.8	7.1	1.6	7.2	29.8	26.6
≥ 60	7,056	46.1	24.3	5.9	24.4	37.0	37.3
Chi-square		209.61	1450.24	308.04	1424.65	271.37	217.34
P value		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

n = number of strains tested.

Table 4 – *Chi-square test for trend applied to E. coli resistance rates (%) to various antimicrobials in 4 surveyed years (2000 to 2003).*

	2000	2001	2002	2003	χ^2 for Trend	p Value
Ampicillin	44.3	41.0	42.8	45.0	0.243	0.6
Ciprofloxacin	9.3	10.8	13.5	14.0	77.366	< 0.0001
Nitrofurantoin	3.1	2.4	3.5	2.7	0.550	0.5
Norfloxacin	9.4	10.9	13.7	14.0	76.736	< 0.0001
Tetracycline	35.0	29.9	29.6	28.9	98.600	< 0.0001
Trimeth-sulfa	33.5	33.0	34.3	33.6	0.384	0.5
Nalidixic acid	13.1	14.3	17.2	17.4	51.520	< 0.0001

In the present study, among the 22,679 E. coli tested, the resistance rate to trimethoprim-sulfamethoxazole was 33.7%. Additionally, 11.9% of the E. coli were resistant to ciprofloxacin, 12.0% to norfloxacin and 15.5% to nalidixic acid. Amongst the gram-positive isolates, E. faecalis presented considerable resistance to ciprofloxacin (16.1%). Although with a different methodology, the present study demonstrated similar E. coli resistance rates when compared to the Hummers-Pradier clinical study (15); nevertheless E. faecalis showed a marked difference in the resistance rate to ciprofloxacin (82.8%) if compared to the same study (15). There were also significant differences in the E. coli resistance rates to trimethoprim-sulfamethoxazole in comparison to recent studies from other environments, which reported rates from 15-25% in a surveillance (6) and a clinical study (16), and from around 2-15% on isolates with a single cross-resistance in another surveillance study (17). This study showed that nitrofurantoin was very active against isolates of E. coli and E. faecalis but not against K. pneumoniae, similar to other studies (6,15-18).

Furthermore, the present study detected that resistance rates of E. coli, P. mirabilis and K. pneumoniae to ceftriaxone were 0.3%, 0.4% and 1.7%, respectively. A possible explanation to this fact might be the presence of Extended Spectrum Beta-Lactamases (ESBL) in these strains (all of them in the age groups over 4 years old - data not shown). This finding suggests the existence of non-community acquired infections among the population under surveillance (possibly but not exclusively nursing homes and home-care facilities), which may have tests performed in the present centre. It is worth to mention that ceftriaxone is not the best screening drug for ESBLs and this was not the objective of this study. However, this is a relevant finding, since it might indicate that infections with these types of strains are being detected in outpatients in Brazil - although further confirmation and stratification for risk factors are needed.

As seen in Table-3, E. coli resistance rates for ciprofloxacin and norfloxacin were 24.3% and 24.4% respectively in the age group of ≥ 60 years old, while it was below 8% for both drugs in all other age groups. It was also noticed a variation of E. coli resistance rates to ampicillin and trimethoprim-sulfamethoxazole between age groups, with higher rates seen in the age groups below 13 years old. As for tetracycline, E. coli resistance rates ranged from 26.6% to 37.3%, showing generally more elevated resistance levels among all age groups; although with a particular higher resistance rate seen in the age group ≥ 60 years old. Finally, nitrofurantoin showed low resistance rates in all age groups, with a higher rate observed for this drug in the group ≥ 60 years old (5.9%).

Additionally, the chi-square test for trend shown in Table-4 has demonstrated apparently stable resistance rates to nitrofurantoin, ampicillin, and trimethoprim-sulfamethoxazole ($P > 0.5$), though ex-

tremely higher rates to the latter two drugs. On the other hand, increasing resistance rates to ciprofloxacin, norfloxacin, and nalidixic acid ($P < 0.0001$) have been detected, with approximately 9.0% resistance to ciprofloxacin and norfloxacin in 2000 and 14.0% in 2003. Surprisingly, an ordered decline of the resistance rate to tetracycline was observed, with 35.0% in 2000 and 28.9% in 2003 ($P < 0.0001$). These data may have many interpretations, among them a possible changing pattern of antimicrobial use in the population within the period surveyed, with increased use of fluoroquinolones and decreased use of other drugs, particularly in the older population. However, if these findings are due to other factors different from the suggested ones, such as clonal dissemination, as described by Manges et al. (19), or methodological limits, remains to be determined by further studies.

A final remark must be made on the use of routine antimicrobial susceptibility testing data based on breakpoint concentrations and the limits imposed by the method. Although this has been used before and is acceptable (15), detailed shifts or subtle differences in susceptibility rates may be lost by its use, particularly for agents where susceptible isolates may cluster near a breakpoint. However, it is the opinion of the authors that this would be more problematic in cross-sectional studies, where trends cannot be analyzed and, thus, the same method cannot be compared throughout a certain period.

CONCLUSIONS

Elevated resistance rates in E. coli from urinary tract infections in outpatients to ampicillin, trimethoprim-sulfamethoxazole, and tetracycline preclude the use of these drugs for empirical treatment in the environment evaluated for all age groups. Instead, nitrofurantoin should be used as empirical therapy for primary, non-complicated urinary tract infections (except in patients with impaired renal function) in outpatients of the greater São Paulo area, Brazil. Thus, there is sufficient indication showing that the E. coli resistance trend for fluoroquinolones is increasing, and although not clarified by this study, possibly linked to higher use of this drug class either by the individual and/or by the population. Due to this trend, this class should be used with caution, particularly if no microbiological documentation is available. At last, resistance prevalence studies may be a useful tool for guiding antimicrobial therapy and helping curb resistance due to selective pressure in community-acquired infections, especially UTI.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Carlos R.V. Kiffer
Instituto Fleury, Microbiologia
Avenida General Valdomiro de Lima 508
São Paulo, SP, 04344-903, Brazil
Fax: + 55 11 5014-7601
E-mail: carlos.kiffer@fleury.com.br

EDITORIAL COMMENT

This is an important paper providing susceptibility data on community acquired urinary tract infections (UTI) from a large population. Such information is necessary for working out recommendations on empirical treatment of UTI. Resistant bacterial strains are frequently brought to urology departments by patients with complicated UTI. Therefore, susceptibility data from primary health care is also important information for urologists.

From a European perspective, it is interesting to note that frequently used drugs like mecillinam and fosfomycin trometamol still seem to be unused therapeutic weapons.

Dr. Truls E. Bjerklund Johansen
Chair, European Society for Infections in Urology
Telemark Central Hospital, Urology Section
Porsgrunn, Norway
E-mail: tebj@sthf.no

EDITORIAL COMMENT

Urinary tract infections are among the most common community acquired infections. Whereas in nosocomial urinary tract infections surveillance is frequently performed around the world or even mandatory in some countries, data on outpatients' urinary tract infections are still scarce. This study investigated more than 37,000 urinary isolates of outpatients in the Sao Paulo urban area. Antibiotics such as trimethoprim/ sulfamethoxazole exhibited high resistant rates, which precludes the use of this substance as primary empiric treatment for outpatient urinary tract infections. Additionally there was a significant increase in fluoroquinolone resistance over the last years to levels where treatment failures might occur in significant cases. Studies like this will help to improve and tailor empiric antibiotic treatment for urinary tract infections in the area of Sao Paulo.

Dr. Florian M. E. Wagenlehner
Department of Urology
Justus-Liebig-University Giessen
Giessen, Germany
E-mail: wagenlehner@aol.com

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Wet Heat Exposure: A Potentially Reversible Cause of Low Semen Quality in Infertile Men

Shai Shefi, Phiroz E. Tarapore, Thomas J. Walsh, Mary Croughan, Paul J. Turek

Departments of Urology (SS, PET, TJW, PJT), Obstetrics, Gynecology and Reproductive Science (MC, PJT), and Epidemiology and Biostatistics (MC), University of California San Francisco, San Francisco, California, USA

ABSTRACT

Objective: To evaluate the recovery of semen quality in a cohort of infertile men after known hyperthermic exposure to hot tubs, hot baths or whirlpool baths.
Materials and Methods: A consecutive cohort of infertile men had a history remarkable for wet heat exposure in the forms of hot tubs, Jacuzzi or hot baths. Clinical characteristics and exposure parameters were assessed before exposure was discontinued, and semen parameters analyzed before and after discontinuation of hyperthermic exposure. A significant seminal response to withdrawal of hyperthermia was defined as ≥ 200% increase in the total motile sperm count (TMC = volume x concentration x motile fraction) during follow-up after cessation of wet heat exposure.
Results: Eleven infertile men (mean age 36.5 years, range 31-44) exposed to hyperthermia were evaluated pre and post-exposure. Five patients (45%) responded favorably to cessation of heat exposure and had a mean increase in total motile sperm counts of 491%. This increase was largely the result of a statistically significant increase in sperm motility from a mean of 12% at baseline to 34% post-intervention (p = 0.02). Among non-responders, a smoking history revealed a mean of 5.6 pack-years, compared to 0.11 pack-years among responders. The prevalence of varicoceles was similar in both cohorts.
Conclusions: The toxic effect of hyperthermia on semen quality may be reversible in some infertile men. We observed that the seminal response to exposure elimination varies biologically among individuals and can be profound in magnitude. Among non-responders, other risk factors that could explain a lack of response to elimination of hyperthermia should be considered.

Key words*: male infertility; induced hyperthermia; semen; analysis; spermatogenesis*
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INTRODUCTION

Spermatogenesis is sensitive to a variety of chemical and physical stressors. Testicular hyperthermia has been known to have a deleterious effect on male fertility since the time of Hippocrates and is a well-recognized cause of impaired sperm production (1). Its detrimental effect has been demonstrated in both animal models and in humans (2-4). Whether due to endogenous (such as high fevers) or exogenous stimuli, heat decreases sperm concentration, impairs motility, and reduces the number of morphologically normal sperm (5-8). This effect is striking enough that the effect of laptop computers on scrotal hyperther-

mia has recently been reported and the use of heat exposure as a male contraceptive has been studied (9,10). In contrast to the well described detrimental effects of dry heat on spermatogenesis, the consequences of wet heat exposure are relatively undefined. Our working hypothesis is that the effects of wet heat on spermatogenesis are similar to that from dry heat.

The only published study to examine the effects of wet heat exposure on human fertility was performed by Rock and Robinson in 1965. In this study, the authors exposed 20 oligospermic men to wet heat (43-45°C) with a bottle warmer held between the thighs for 30 minutes on 6 alternating days. They noted a decline in sperm production that was followed by improvement in seminal parameters with cessation of the exposure, however the details of semen quality before and after exposure were not provided by the authors (11). The effects of more common exposures to wet heat, such as with hot tubs, Jacuzzis, or hot baths have not been addressed in the literature.

The data provided by Rock and Robinson, as well as the well-defined association between dry heat exposure and impaired spermatogenesis led us to study the effect of total-body wet heat exposure in human males. We asked whether withdrawal of exposure in men with poor semen quality and a history of wet heat exposure could lead to an improvement in semen quality. We retrospectively compared semen quality before and after cessation of wet heat exposure, and also performed an interval analysis of responders and non-responders, looking for factors that might modulate responsiveness to therapeutic intervention.

MATERIALS AND METHODS

Over a 3-year period, infertile men with exposure to wet heat were identified in a single, university-based, male infertility practice. Inclusion criteria were wet heat exposure, defined as the immersion of the body in a hot tub, heated Jacuzzi, or bath at a temperature warmer than body temperature, for ≥ 30 minutes per week during ≥ 3 months prior to presentation. All female partners were concurrently assessed for reproductive issues. Patients were excluded if they had received any medical or surgical infertility treatment within 1 year of study intake, and if a diagnosis of co-existing female factor infertility was made. Because patient data was decoded of all protected health information, a waiver was obtained from the Committee on Human Research for this study.

All subjects underwent a complete history and physical examination by a single specialist (PJT). Information regarding the type, frequency, duration/episode and overall length of exposure to wet heat was collected during this visit. Counseling regarding the cessation of wet heat exposure was given during the initial visit. We attempted to obtain 2 semen samples for analysis at baseline (during exposure), < 3 months after intervention, and between 3-6 months after intervention in all patients. Semen was collected by masturbation after 2 to 3 days of abstinence and processed within 1 hour of ejaculation. All semen analyses were performed in a single andrology laboratory by the same technician, and assessed according to World Health Organization guidelines (12). Motility was reported as the sum of A + B patterns (12). A positive response to discontinuation of heat exposure was defined as an increase in total motile count (TMC = ejaculate volume x sperm concentration x fraction of motile sperm) > 200% during follow-up. This cutoff was selected to be above the natural variability in semen parameters within an individual: sperm volume, concentration and motility have been shown to vary by 59%, 54% and 96%, respectively, in a single individual with time (13). Statistical analysis was performed using two-tailed, paired "t" test to compare pre- and post-intervention seminal parameters. Probability values < 0.05 were considered significant.

RESULTS

Patient Characteristics

Table-1 outlines the demographic and clinical characteristics of the 11 eligible study subjects. Mean patient age was 36.5 years, and mean partner age was 34.6 years. Couples had been trying to conceive for an average of 2.6 years (range 0 - 15 years) prior to evaluation. Nine patients (82%) had an evi-

Table 1 – *Characteristics of the study group.*

Characteristic	Mean ± SD	Range
Patient age (yr)	36.5 ± 4.5	31 - 44
Partner age (yr)	34.6 ± 6.4	22 - 42
Time attempting (yr)	2.6 ± 4.3	0 - 15
Exposure (min/week)	148.6 ± 82.3	60 - 315
Exposure history (yr)	2.9 ± 3.3	0.75 - 10
R-testis volume (mL)	16.9 ± 3.7	10 - 20
L-testis volume (mL)	17.0 ± 4.9	8 - 25
Smoking (pack-year)	3.1 ± 5.5	0 - 15

Testicular volume was determined using Prader orchidometer.

dence of infertility, defined as failure to conceive after one year of unprotected sexual intercourse. The mean exposure duration was 149 minutes per week (range 60 - 315), with a mean total duration of hyperthermic exposure of 2.9 years (range 0.75 - 10). Five subjects were exposed to hot baths, 4 to both hot baths and hot tubs, and 2 to Jacuzzi. Three of the 11 subjects had a significant smoking history (> 6 pack-years). Five others were only occasional smokers (< 1 pack-years). Complete pre-intervention semen parameters among study subjects are given in Table-2. Patients had an average of 1.6 ± 0.6 and 2.5 ± 1.7 semen analyses performed prior to cessation of exposure and following cessation, respectively. Nine men (82%) had TMC < 20 x 10^6 (mean 5 x 10^6). The other 2 men had TMC's of 34 x 10^6 and 117.6 x 10^6 sperm.

Table 2 – *Seminal parameters before intervention.*

Characteristic	Mean ± SD	Range
Ejaculate volume (mL)	3.3 ± 1.3	1.3 - 5.3
Sperm concentration (x 10^6/mL)	15.8 ± 16.0	0.2 - 42.5
Sperm motility (%)	23.8 ± 20.6	0 - 70
Total motile sperm count (x 10^6)	17.9 ± 34.5	0 - 118

Response to Cessation of Wet Heat Exposure

Semen analyses for each subject were categorized into baseline (during exposure), 0 to 3 months post-intervention, and > 3 months post-intervention. Multiple semen analyses within a given period were averaged for each individual during that period. Sperm parameters before and after discontinuation of exposure are listed in Table-3. TMC values and response to intervention status are shown in Table-4. Mean follow-up of the study cohort was 7 months (range 2-16). Amongst the entire cohort, improvement in TMC did not reach statistical significance (p = 0.89). Overall, 44.5 % (95% CI 16.7,76.7) of men showed > 200% increase in total motile sperm count after discontinuation of wet heat

Table 3 – *Semen parameters at baseline, 0-3 months post-intervention, and more than 3 months post-intervention.*

	Baseline			0-3 months			3+ months		
Pt. No	Volume (mL)	Concentration (x 10^6/mL)	Motility (%)	Volume (mL)	Concentration (x 10^6/mL)	Motility (%)	Volume (mL)	Concentration (x 10^6/mL)	Motility (%)
1	3.0	3.0	34	2.4	14.9	24	1.8	12.0	44
2	5.3	10.5	17	3.5	18.0	62	-	-	-
3	4.4	0.7	23	4.5	0.7	15	1.8	1.5	7
4	4.0	42.0	70	2.5	63.0	55	-	-	-
5	1.7	0.2	0	0.8	1.0	23	-	-	-
6	4.2	9.5	37	6.0	7.0	23	4.6	9.0	32
7	2.0	42.5	40	-	-	-	1.0	21.0	40
8	2.5	13.0	9	3.5	21.0	3	-	-	-
9	4.8	9.0	24	4.5	5.0	26	5.5	5.4	21
10	3.4	8.9	2	3.3	15.0	36	3.6	19.0	19
11	1.3	35.0	7	1.3	14.0	4	2.1	32.4	22

Table 4 – *TMC (x 10^6)* at baseline, 0-3 months post-intervention, and > 3 months post-intervention.

Pt. No.	Baseline	0-3 months	3+ months	Change (%)	Responder
1	2.9	10.1	9.3	+ 221	Yes
2	9.5	39.1	-	+ 312	Yes
3	0.6	0.7	0.2	- 67	No
4	117.6	86.6	-	- 26	No
5	0	0.2	-	+ ∞	Yes
6	14.4	9.7	13.2	- 8	No
7	34	-	8.4	- 72	No
8	2.9	1.8	-	- 38	No
9	10.4	5.9	5.5	- 47	No
10	1.1	17.8	10.7	+ 873	Yes
11	3.2	0.7	21.1	+ 559	Yes

TMC = total motile sperm count, % change: based on last available data compared to baseline for each individual. Response was defined as an increase of TMC ≥ 200%.

exposure and were considered responders to intervention.

Among responders, the mean increase in TMC was 491% (range 221-873), excluding an outlier whose TMC improved from zero to 200,000 sperm. Responders' TMC before and after intervention are illustrated in Figure-1. The seminal response in the responding cohort showed increases in sperm concentration, but largely the result of increases in sperm motility. Although the increase in TMC increase did not reach statistical significance (p = 0.07) among responders, a subset analysis showed a mean increase of 22% in sperm motility, which was statistically significant (p = 0.02). Among responders, one patient had a TMC increase from 0 to 0.2 million sperm, two patients had post-intervention TMC's of 9.3 and 10.7 x 10^6, while two more had a TMC's of > 20 x 10^6 sperm. There was no significant difference in the length of follow-up among study responders and non-responders.

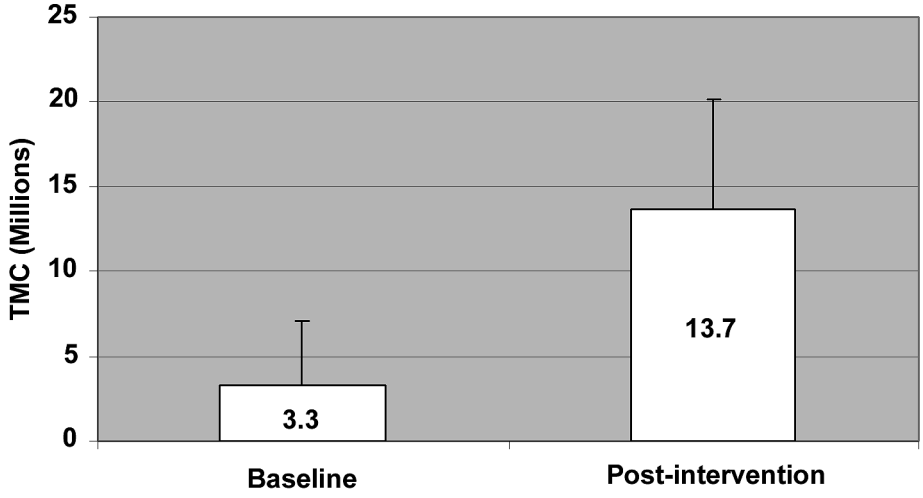

Figure 1 – *Mean total motile count (TMC) in responders cohort for baseline and > 3 months post-intervention. Bars represent standard deviation.*

Factors that could explain a response or lack of response to the intervention were examined in both cohorts. Tobacco use emerged as a possible differentiating factor. Among 6 non-responders, 5 were chronic tobacco users with a significant smoking history (mean 5.6 pack-years), compared with 3 occasional smokers in the responder group, whose mean tobacco consumption was 0.11 pack-years. The prevalence of varicoceles was similar in responders and non-responders (4/5 and 4/6 patients, respectively). No other potential gonadotoxic factors were identified in the study cohort.

COMMENTS

The removal of wet heat exposure resulted in improvement in semen quality in nearly one-half of subjects studied. The improvement was largely the results of increases in sperm motility, and appeared to persist beyond 3 months, although a continuous improvement was not observed in all subjects. The extra-abdominal position of the scrotum and the proximity of the pampiniform venous plexus to the testicular arteries contribute to the efficient dissipation and transfer of heat away from the testes and resultant lower testicular temperature (8). However, in the presence of extreme elevation of extra-testicular temperature, as when immersed in hot liquid, these same characteristics make the scrotum particularly susceptible to deleterious thermal effect. It is therefore not surprising that semen quality might be susceptible to the effects of wet hyperthermia.

The deleterious effect of dry heat on semen quality and, by extrapolation, male fertility, has been recognized medically for decades, and to the traditional medicine community for millennia. Carlsen et al., in examining the effect of febrile illness on semen quality, demonstrated a dose-response relationship between the number of days with fever and sperm concentration (8). Similarly, Mieusset & Bujan examined mild testicular heating (about 1°C) as a form of contraception, an idea originally conceived of by Robinson et al. (14,15). Both studies found that sperm concentration rebounded to baseline in 12 to 18 months following cessation of increased testicular temperatures. None of these studies, however, were designed to replicate the frequent, significant wet hyperthermia that is the fate of the habitual hot-tuber, thus forming the rationale for this study.

In reviewing our data on the recovery of semen quality in infertile males following the cessation of wet heat exposure, we found that there were two distinct groups of patients: those that responded to intervention and those that did not. Among responders, improvements in semen quality were witnessed well beyond the 3 month period typically ascribed to a single cycle of spermatogenesis. This finding is entirely consistent with the time course of recovery noted after varicocele repair and exposure to other gonadotoxins (16). Interestingly, the semen analysis parameter that exhibited the largest change among responders was sperm motility, and this increase reached statistical significance after intervention. This suggests that heat-induced motility dysfunction may be the parameter most vulnerable to wet hyperthermic exposure. Although statistical significance was not achieved in the overall increase in TMC after intervention, the changes observed could be considered clinically significant, as more men could qualify for IUI instead of IVF for infertility treatment following intervention. Given that intrauterine insemination (IUI) can be considered for low semen quality in men with TMC > 8-10 x 10^6 sperm, the number of men who would qualify for IUI in the responder group increased from 1/5 pre-intervention to 4/5 post-intervention. Two of the responders had TMC > 20 x 10^6 after intervention and were advised to consider unprotected intercourse before IUI. This "shift of care" to less intensive forms of assisted reproduction has also been described for varicocele repair (16). We acknowledge that even statistically significant changes in semen parameters are always problematic to assess, given the naturally high intra-individual variability of semen parameters in both fertile and infertile men. However, the potential clinical value of these changes must also be considered, as we have outlined.

Careful analysis of non-responders suggests that chronic tobacco use was more common among non-responders, suggesting that it may complicate the recovery from wet heat exposure. This finding is hardly surprising, considering that tobacco use is a

well established, independent risk factor for poor semen quality (17-19). It is interesting to speculate whether the concomitant exposure to tobacco and wet heat may act synergistically to prevent early and rapid recovery of semen quality.

It is interesting that two responders demonstrated subtle declines in TMC following the 3-month time interval. This lack of continuous improvement suggests that peak improvements in TMC may be time-limited and could involve other, less well-described physiological responses. It may also suggest that a timeline for therapy be offered to affected patients, to avoid prolonged follow-up without obvious benefit.

Because this is a small study, the results should be confirmed in a larger series of patients. Given the complexity of factors underlying male infertility, including currently uncharacterized factors, more accurate results will only be generalizable with a larger study. We plan further follow-up on the patients in this study to assess conception after elimination of hyperthermia.

CONCLUSIONS

This study addressed the relatively unsubstantiated issue of wet heat exposure as a factor in male infertility. We demonstrated that infertile men who are frequently exposed to wet heat in the form of hot tubs, Jacuzzis, or hot baths, may realize a marked increase in semen quality following cessation of exposure. The response persists for more than 3 months, and is driven mostly by the increase in sperm motility.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Paul J Turek
Department of Urology, UCSF
1600 Divisidero St, Rm A633
San Francisco, CA, 94143-1695, USA
E-mail: pturek@urology.ucsf.edu

EDITORIAL COMMENT

Numerous factors can elevate scrotal temperature either by whole body or local scrotal heating. Scrotal hyperthermia was found in men with febrile illness, retractile testes, occupations associated with high temperature exposure, hot bath and sauna users, men wearing tight jockey shorts, car drivers, and laptop computer users. Multiple human studies have confirmed deleterious effect of increased scrotal temperature on sperm quantity and quality.

The authors investigate a less defined effect of total body wet heat exposure (hot tub, heated Jacuzzi or bath) on spermatogenesis. While studied population is very small and most results are not statistically significant, this article presents evidence of occasional reversibility of negative thermal effect and improvement of total motile sperm count and motility after cessation of heat exposure within the predictable interval of 3 months. However, time to maximum effect and durability of improvement also remain unclear due to a short follow-up period.

Despite significant limitations the study is noteworthy since it emphasizes important but frequently omitted details in the evaluation and management of the infertile men: 1) It is necessary to ask patients about habitual and occupational heat exposure, 2) It is worthwhile to recommend cessation of confirmed frequent heat exposure and repeat semen analysis within 3 month interval. Improved sperm quantity and quality in select patients may "upgrade" their treatment from IVF to IUI or, possibly, from IUI to natural pregnancy.

Finally, since such improvement, its magnitude and durability are not predictable, watchful waiting approach has to be exercise within strictly defined and limited time which will not delay other recommended treatment options.

Dr. Yefim R. Sheynkin
Associate Professor of Clinical Urology
State University of New York at Stony Brook
Stony Brook, New York, USA
E-mail: ysheynkin@notes.cc.sunysb.edu

REPLY BY AUTHORS

Although talked about for decades, the detrimental effect of hot tubs, Jacuzzis and hot baths on semen quality and male fertility has never been formally investigated, and forms the rationale for this study. As a result, we now have actual evidence to show patients that these recreational activities are a real risk factor for male subfertility. In addition, these activities can be comfortably added to that list of lifestyle recommendations and "things to avoid" as men attempt to conceive.

We believe that the finding of significantly improved semen quality in almost half of study patients is certainly evidence of an exposure effect that is more than just "occasional," as suggested above. And let us examine the clinical impact of this finding bit closer. How could the ability of a simple lifestyle maneuver that can "shift the care" from higher (IVF-ICSI) to lower and less expensive forms of assisted reproduction (IUI) not have the potential for enormous clinical impact given the cost of treating human subfertility? Just ask patients!

What we also find provocative is the discussion of possible clinical features that might impair the response to wet heat elimination (i.e. varicocele and tobacco use). Given the complexity of factors underlying male infertility, including currently uncharacterized issues, we agree that stronger, more generalizable statements regarding this particular exposure and its effect on male infertility can only be made with a larger study.

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The Isolated Gamma Probe Technique for Sentinel Node Penile Carcinoma Detection Is Unreliable

Lucio F. Gonzaga-Silva, Jose M. Tavares, Fernando C. Freitas, Manoel E. Tomas Filho, Vladmir P. Oliveira, Marcos V. Lima

Department of Surgery, Federal University of Ceara and Section of Urology, Cancer Hospital of Ceara, Fortaleza, Ceara, Brazil

ABSTRACT

Purpose: Penile carcinoma is a common disease in northeast Brazil. This paper shows the results of the use of isolated gamma probe and discusses the incidence of false negative rates.
Materials and Methods: From July 2000 to September 2003, 27 newly diagnosed penile carcinoma patients (T1, T2, N0) were included in this prospective study. The isolated gamma probe technique uses the sodium phytate technetium as a tracer and inguinal scanning with probe and after identified the lymph node it is removed. Lymphadenectomies were performed for positive inguinal lymph nodes metastasis.
Results: There were 27 patients (mean age 59.6). Follow up was 37 months. Patients from country were 72% and illiterate or semi-illiterate were 56.7%. The tumors were mostly located in the glans (81.4%). They were T1, 52 % and T2, 48 %. 81.4% of the patients underwent partial penectomy, and 18.6% underwent postectomy and excision with wide margins. In 48% of the patients, the highest radioactive count rate was located on the left side, while in 41% was located on the right side. Only one patient had a positive pathological lymph node metastasis at the moment of the surgery. Additionally 3 patients became inguinal lymph node positive at the follow up. This date yielded a sensibility rate of 25% and a false-negative rate of 42.8%.
Conclusion: Isolated gamma probe technique for sentinel node penile carcinoma has a very low sensibility and a high false negative rate. Therefore it is highly advisable the addition of others methods such as lymphoscintigraphy, vital blue, ultrasonography and so on. The isolated gamma probe technique for sentinel node penile carcinoma detection is unreliable.

Key words*: penile cancer; lymphatic metastasis; sentinel lymph node biopsy; gamma probe technique*
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INTRODUCTION

Though rare in developed countries, penile carcinoma is relatively common in Latin America (1). On the average, 3 new cases have been identified at our Hospital every month over the last 5 years (2).

The lymphatic system is the primary route for metastasis. Tumors spread loco-regionally and stepwise (3). Survival of patients with penile carcinoma clearly depends on the status of the inguinal lymph node (4). Thus, the overall 5-year survival rate is 73-95% for patients with negative inguinal lymph

nodes and 19-62% for patients with positive inguinal lymph nodes (5). When associated with pelvic disease, the 5-year survival rate is less than 10%. If left untreated, patients with metastasis rarely survive for longer than 2 years (6).

In patients with metastasis confined to the regional lymph nodes, inguinal lymphadenectomy is very often curative, with disease-free rates of 30-90% (7). Inguinal lymphadenectomy has been associated, in some reports, with significant levels of morbidity (30-50%) and up to 3% of mortality (8,4). Moreover, prophylactic bilateral inguinal lymph node dissection is considered unnecessary in up to 80% of penile carcinoma patients with clinically negative regional lymph nodes (9).

Elective bilateral inguinal lymph node dissection is the most invasive approach and the least invasive is a "wait and see" policy (10). However, the latter is associated with a poorer prognosis if tumor-involved lymph nodes become palpable during follow-up (11,12).

Dynamic sentinel node biopsy provides a means of assessing lymph node status in the management of penile carcinoma, through a minimally invasive procedure. It has important diagnostic, prognostic and therapeutic value at the cost of only minor morbidity and is an attempt to diminish the risk of complications without jeopardizing the oncological results (10).

The gamma probe technique has been adopted at our institution since July 1999. However, it was used alone (without lymphoscintigraphy and vital dye) on the first 27 patients mainly because our hospital had not yet been officially authorized to use the gamma camera.

After the use of the equipment had been authorized (September 2003), the complete approach (gamma probe, lymphoscintigraphy and vital blue dye) became the routine procedure in the investigation of penile carcinoma sentinel nodes.

The purpose of this paper was to show the results of the isolated use of gamma probe technique for sentinel node investigation in patients with penile carcinoma at our institution, before the complete technique was introduced in September 2003, and to analyze its value as a less invasive lymphatic staging method.

MATERIALS AND METHODS

Between July 2000 and September 2003, 27 patients with newly diagnosed penile squamous cell carcinoma were prospectively enrolled for sentinel node detection by gamma probe technique. Informed consent was obtained from all patients and the protocol was approved by the research ethics committee at our institution.

The 27 patients enrolled in the study did not differ significantly from subjects described in similar studies published in the literature. The mean age was 59.6 years (range 41-80). The Mean follow-up time was 37 months (range: 24-62). Five patients were lost to follow up (Table-1).

Patients were eligible when staged T1-T2, N0, according to the 2002 TNM classification system of the International Union Against Cancer.

At our hospital, technetium-99-m-labeled sodium phytate (99mtc) is used in colloidal presentation as a tracer. A dose of 0.2 mL was injected subdermally at the four cardinal points around the penile lesion, totaling 0.8 mL. The average radioactive dose was (59 MBq) (13).

The bilateral inguinal probe scanning was performed about 30 minutes after the injection. First, background count is established by measuring radioactivity over a neutral site. Then the handheld gamma detection probe was used to identify the sentinel node sites. A sentinel node was defined as a node with radioactivity three times over the background.

Finally, the focus of activity in the inguinal area (the so-called hot point) was marked off. A small incision was then made and the sentinel node was removed. When sentinel lymph nodes are removed successfully, the radioactivity count rate on the excision site should not exceed 10% of the highest ex-vivo radioactivity count.

The excised sentinel lymph node was sent to the pathologist after making sure it was the one (on either side) with the highest background radioactivity count (corresponding to the highest quantity of radio colloid).

The sentinel node was bisected, fixed in formalin, embedded in paraffin and sectioned at 8 lev-

els, on the average (5-μm sections). Paraffin sections were stained with hematoxylin and eosin (13).

Inguinal lymphadenectomies were performed immediately for all inguinal lymph node metastasis proving positive. Negative cases, (i.e. without lymph nodes metastasis) were followed up with check-ups every three months for three years. Patients subjected to inguinal lymphadenectomy were kept under careful observation to identify early or late complications.

Disease-specific survival is defined as the percentage of people in a study who have survived a particular disease (in this case, penile cancer) since diagnosis or treatment. Disease-free survival is the length of time after treatment during which no disease (in this case nodal or distant recurrence) is found.

RESULTS

Most of the patients were illiterate or semi-illiterate (56.7%) (From country 72%). The tumors were mostly located in the glans (81.4%) and in the prepuce (38%). Some tumors affected the glans and prepuce (18.5%).

As to the tumor stage, 51.9% were T1 and 48.1% were T2. With regard to treatment, 81.4% of the patients underwent to partial penectomy, while the remainder had postectomy and excision with wide margins (18.6%). In eleven patients (40.7%), the highest radioactive count was located only on the left side; in nine patients (33.3%), it was located only on the right. The radioactive count was too low for sentinel node identification in three patients (11.1%) (Table-1).

No complications related to the isolated gamma probe technique for sentinel node penile carcinoma detection were observed.

Only one patient exhibited lymph node metastasis at the time of the surgery. The patient was given a bilateral inguinal lymphadenectomy during the same session. The pathological examination of the specimen revealed that the excised sentinel lymph node was the only node affected (Table-1).

In addition, three patients who were negative for pathological lymph node metastasis at the moment of the surgery became inguinal lymph node-positive in the course of follow up. Thus, the sensitivity rate was 25% and the false-negative rate of 42.8% (Table-1).

Of the four patients submitted to bilateral inguinal lymphadenectomy three are disease-free at the time of writing (September 2005) and one died of cancer.

COMMENTS

Prophylactic bilateral inguinal lymph node dissection is considered unnecessary in up to 80% of penile carcinoma patients with clinically negative regional lymph nodes. The challenger lies in identifying the remaining 20% of occult metastasis and thereby offers such patients an opportunity for cure (9).

The isolated use of familiar predictive prognostic factors for the diagnosis of occult lymph node metastasis, such as depth of invasion, differentiation grade, and vascular invasion, results in considerable false-positive and false-negative rates (10).

On the other hand, dynamic sentinel node biopsy has proved very useful in the detection of occult lymph node metastasis. The procedure is minimally invasive, preventing unnecessary lymph node dissections, and moreover, improves substantially the staging with a morbidity rate of only 8% (10,14).

Although dynamic sentinel node biopsy for penile carcinoma was adopted at our hospital in July 2000, the procedure was restricted to the intra-operative gamma ray technique. Twenty seven patients were studied by this method until September 2003 when the complete technique (including preoperative lymphoscintigraphy, intra-operative gamma ray detection and a vital blue dye) became available.

Sentinel lymph node biopsy is best performed by a committed team with experience in surgery, pathology and nuclear medicine. The nuclear physician is responsible for preparing and measuring the radioactive material and for controlling the measuring and mapping equipment. The surgeon is responsible for handling the probe during the surgery, for the surgical procedures and for the management of the case during follow-up (15).

Table 1 – *Patients age, overall findings, treatment and follow up.*

Patient (age)	Probe	Histology		Staging	Treatment	DS	Follow up
1 (74)	(+) L (uni)	(-)		T2	PP	DF	62 m
2 (61)	(+) L (uni)	(-)		T2	PP	DF	53 m
3 (49)	(+) R (uni)	(-)		T2	PP	DF	3 m [A]
4 (49)	(-)			T1	Excision	DF	53 m
5 (76)	(+) R (uni)	(+)		T1	PP / IBL	DF	52 m
6 (46)	(+) B (bil)	(-)	(+)	T2	Em / IBL	DF	52 m
7 (63)	(+) B (bil)	(-)	(+)	T1	PP / IBL	DF	15 m [B]
8 (66)	(+) R (uni)	(-)		T2	PP	DF	50 m
9 (52)	(+) L (uni)	(-)		T1	PP	DF	48 m
10 (69)	(+) B (bil)	(-)		T2	PP	DF	48 m
11 (54)	(+) L (uni)	(-)		T1	Excision	DF	39 m
12 (41)	(+) L (uni)	(-)		T2	PP	DF	06 m [C]
13 (55)	(+) L (uni)	(-)		T2	PP	DF	40 m
14 (63)	(+) B (bil)	(-)		T1	PP	DF	39 m
15 (76)	(+) L (uni)	(-)		T2	PP	DF	22 m [D]
16 (80)	(+) R (uni)	(-)		T1	PP	DF	37 m
17 (64)	(+) L (uni)	(-)		T2	PP	DF	33 m
18 (42)	(+) L (uni)	(-)		T1	P	DF	33 m
19 (46)	(-)			T1	PP	DF	31 m
20 (60)	(+) R (uni)	(-)	(+)	T2	PP / IBL	Ca Death	
21 (60)	(+) L (uni)	(-)		T1	PP	DF	31 m
22 (63)	(+) R (uni)	(-)		T1	PP	DF	30 m
23 (50)	(+) R (uni)	(-)		T1	Mohs surgery	DF	30 m
24 (74)	(+) R (uni)	(-)		T2	PP	AD Death	
25 (73)	(-)			T2	PP	DF	1 m [E]
26 (74)	(+) L (uni)	(-)		T1	PP	DF	26 m
27 (72)	(+) R (uni)	(-)		T1	PP	DF	24 m

N = 27 patients; probe (+) = background count positive; probe (-) = background count negative; DS = disease status; DF = disease free; Ca death = Cancer death, AD Death = death for another disease; L = left side; R = right side;B = both sides; uni = unilateral; bil = bilateral; PP = partial penectomy; P = postectomy; Em = emasculation; IBL = inguinal bilateral lymphadenectomy; m = months; A = last follow up = May/2001; B = last follow up = Sep/2002; C = last follow up = Nov/2002; D = last follow up = Feb/2003; E = last follow up Oct/2003. Patients 6,7 and 20 developed inguinal tumor during the follow up (7,8 and 6 months).

The overall findings, treatment and follow-up of these initial 27 patients (examined with intraoperative gamma probe only) are illustrated in the Table-1.

Unlike the studies by Horenblas (14), which excluded patients with T1 tumors in view of the low risk of occult metastasis, our study was designed so as to include patients with penile carcinoma staged both T1 and T2 N0, considering the local incidence of late recurrences in such patients (T1).

The Table-1 shows that in all but three patients the sentinel nodes were visualized by the intraoperative gamma probe technique. At this point, no measures were taken for patients with radioactive count below the background count rate (3 patients). However, as recommended by Horenblas and coworkers, it is now considered mandatory to examine such patients for tumor deposits blocking the passage of tracer (5).

The vast majority of our patients underwent to partial penectomy, while three patients with very small tumors (4, 11 and 23) were given conservative surgery. Our research team soon is publishing a description of this approach and its indications.

Only one of 27 T1 and T2 patients had a positive histology test (5). He was submitted to inguinal bilateral lymphadenectomy shortly after penectomy, and was alive and disease-free after a follow-up of 36 months.

The Table-1 shows the number of positive histology tests observed during the total follow-up period (July 2000 to September 2003). The histological positivity was observed in four patients. Thus, the sensitivity of the isolated intraoperative gamma probe technique was 25%.

Inguinal tumor outgrowth after excision of a classified tumor-negative sentinel node or non-visualization is classified as false-negative result (10). The Table-1 show that three patients presented these features i.e. three patients (6,7 and 20) developed inguinal tumor after a negative sentinel node biopsy.

The false-negative rate is defined as the number of false-negative results divided by the total of positive results plus the false-negative results (10). Our three false-negative results occurred clustered around the beginning of the study and resulted in a false-negative rate of 42.8%.

A false-negative rate of this order clearly indicates that the isolated gamma probe technique is not a reliable way of detecting sentinel nodes in penile carcinoma.

The Netherlands Institute of Cancer (Horenblas et al.) found an initial false-negative rate of 18% (6 of 34 cases). The technique revealed metastasis in 28 of 123 patients and was false-negative in 6 patients (13).

In 2001 important adjustments were made to the procedure of dynamic sentinel node biopsy in penile carcinoma patients at the Netherlands Institute of Cancer (Pathological analysis by serial sectioning and immunohistochemical staining, preoperative ultrasonography with fine-needle biopsy aspiration cytology and preoperative lymphoscintigraphy besides exploration of nonvisualized groin) leading to eradication of false-negative results.

In a study of 70 T2-T3 patients submitted to dynamic sentinel node biopsy (pre-operative lymphoscintigraphy, intra-operative gamma probe and vital blue dye), Perdoná and coworkers (2005) found a false negative rate of 11% and a sensitivity of 90% (16).

At our Hospital we had also made adjustments to the procedure (as of September 2003), which now includes preoperative lymphoscintigraphy and intra-operative injection of vital blue dye besides gamma ray detection. These improvements are expected to reduce false-negative rates.

Several studies are presently conducted on a variety of tumors and sites. These studies will no doubt, cautiously endorse sentinel lymph node biopsy. However, sentinel lymph node biopsy can be difficult to master. Most surgeons will agree that it takes considerable experience to correctly identify sentinel lymph nodes; in fact, the Oncology Group of the American College of Surgeons recommends that physicians perform at least 30 sentinel lymph node biopsies as part of their training (17).

CONCLUSION

Our findings show that the isolated gamma probe technique for sentinel node penile carcinoma is associated with very low sensitivity (25%) and high false-negative rates (42.8%). The inclusion of other techniques, such as lymphoscintigraphy, vital blue, ultrasonography, is therefore highly advisable.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Lucio Flavio Gonzaga Silva
Rua Dr. José Lino, 141 / 1002, Varjota
Fortaleza, CE, 60165-270, Brazil
E-mail: gonzagalf@secrel.com.br

EDITORIAL COMMENT

In 1994, we started with sentinel node biopsy for penile cancer patients. While acknowledging the pioneering work of Cabanas we deliberately labeled our procedure as a dynamic sentinel node procedure to underscore the static nature of the original description and the dynamic nature of the new one. The dynamism is readily seen on the lymphoscintigrams, giving an almost real-time picture of the individual drainage pattern. Too many individual variations led to false negative findings, explaining the lack of enthusiasm of the original description of the procedure.

There has been a long controversy between proponents of an early lymph node dissection and proponents of a wait and see strategy for clinically node negative patients. An analysis from our institute showed an increased survival for patients who underwent an early lymph node dissection based on tumor positive sentinel node finings. In these series no unnecessary lymph node dissections were done. All patients harbored pathologically proven clinically occult metastases. Lymph node dissection was done at the earliest possible moment (1).

The main problem remained to improve the accuracy of the sentinel node biopsy. Accurate sentinel node biopsies rely on collaboration of nuclear medicine physicians, surgeons and pathologists. Moreover, it relies on the use of all possible methods to exclude false negative findings. In our practice this means preoperative ultrasound with or without fine needle aspiration biopsy, a preoperative lymphoscintigram, marking of the sentinel nodes on the skin, discussing the lymphoscintigram with the nuclear medicine physician, injecting patent blue around the tumor, using a gamma detector and having a protocol for measurements before removal and after removal, palpation of the wound after removal and a strict pathology protocol. With all these refinements, we were able to bring down the false negative rate of the initial series of 22% to an acceptable 4.8% (in press European Urology). In our hands sentinel node biopsy for penis cancer has evolved as an important clinical staging tool just as reliable as in melanoma and breast cancer patients. One should realize however, that the procedure was initiated in a specialized cancer center together with surgical oncologists, who pioneered the procedure for breast cancer and melanoma.

Another aspect not often cited is the small size of the Netherlands, making regular outpatient-clinic visits easy, follow-up very reliable, with a 100% literacy within the population and the increasing tendency to centralize management of penile cancer patients. All these aspects have been helpful in developing, analyzing and improving the dynamic sentinel node biopsy.

How different is the situation in Brazil and many other countries. The procedure should be viewed against the above-mentioned elements. A rational choice should be made between the introduction of a sentinel node biopsy program, with all the logistics around it or a straightforward lymph node dissection in a patient without any follow up after initial surgery.

What is clear from this paper is that introducing only some aspects of the procedure is not benefiting the patient and should not be done.

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Dr. Simon Horenblas
Professor of Urologic Oncology
Head, Departmen of Urology
Netherlands Cancer
Inst-Antoni van Leeuwenhoek Hosp
Amsterdam, The Netherlands
E-mail: s.horenblas@nki.nl

EDITORIAL COMMENT

Defining the presence (or absence) of microscopic metastases within the inguinal lymph nodes in patients with squamous penile cancer and no clinical lymphadenopathy remains a challenge. Selective lymphadenectomy based upon the stage, grade or the presence of vascular invasion within the primary tumor decreases the incidence of unnecessary lymphadenectomy but is clearly imprecise. Based upon the evolving experience initially published by colleagues at the Netherlands Cancer Institute (ref. 10, 13, 14 in the article) Dynamic Sentinel Lymph Node Biopsy with preoperative lymphoscintigraphy with subsequent intraoperative detection of emitted gamma radioactivity using a hand held probe has been shown to be a minimally morbid procedure.

In the current study, the authors studied a cohort of patients using only intraoperative detection, as preoperative lymphoscintigraphy was unavailable. Four patients were eventually found to exhibit lymph node metastasis but only one of four was discovered at surgery leading to a sensitivity of only 25%. One of the three died due to cancer, one was lost to follow-up at 15 months, and the other is alive and presumed cured at 52 months.

Based upon their experience the authors correctly conclude that gamma detection alone was not sensitive and they have now moved on to performing both lymphoscintigraphy and intraoperative mapping.

This study points to some of the difficulties in establishing a new surgical technique in the setting of a rare disease with a relatively narrow "window of curability". First in their study and those from the Netherland's Cancer Institute (NCI) the patients with false negative findings often present later with incurable disease and die. Second, in the largest series reported the NCI group (using optimal technique) reported a false negative rate of 18% that is almost the same as that reported using physical examination. This has lead to subsequent technical modifications that could improve test performance but this is not guaranteed. Finally the learning curve is thought to be about 30 cases to gain proficiency (ref. 17 in the article) and thus is not practical for most urologists that are not in a referral setting.

Alternatively superficial inguinal lymphadenectomy detects all the first echelon lymph nodes at risk, is less morbid in contemporary reports, and in several reports was not associated with false negative findings (1-3). Thus I believe superficial inguinal lymphadenectomy in selected high risk patients to be the "standard" and Dynamic Sentinel Node Biopsy as reported here, by the NCI group, and in our own experience (ref. 3 below) to be a technique in evolution that is still experimental and requires further refinement in high volume centers.

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Dr. Curtis A. Pettaway
Professor of Urology
The University of Texas
M.D. Anderson Cancer Center
Houston, Texas, USA
E-mail: cpettawa@mdanderson.org

EDITORIAL COMMENT

The presence of nodal metastases is the single most important factor in penile cancer. However, the timing of lymphadenectomy in patients presenting without clinical signs of node disease is still controversial. In the last years, there has been a growing awareness on the need of adopting better staging procedures in order to decrease the number of unnecessary node dissections and to improve detection of occult metastases.

The current European Association of Urology Guidelines recommend a risk-based approach for lymph node staging, including a wait and see strategy and surgical groin exploration using a low, intermediate and high risk stratification (1). In this setting, a new concept for lymph node staging, the so called dynamic sentinel biopsy (DSNB), has been introduced (2). Also in our experience, this technique offered similar results to those of radical lymphadenectomy but significantly lower morbidity (3).

Thus, the present report by Gonzaga-Silva et al. is interesting as it deals with a timely topic in urooncology. Of course, the major limitation of this prospective single institution study is the fact that the authors adopt an incomplete technique, as they clearly admit. This choice is questionable as they offer an already obsolete procedure to their 27 patients, with an expected limited clinical benefit. As a matter of fact, they recognize from the beginning that the real DSNB technique consists of different parts (i.e. preoperative lymphoscintigraphy, blue dye injection, intraoperative gamma ray detection), each one with a specific role in the reliability of the entire diagnostic procedure. They obviously found that the isolated gamma probe use has a very low sensibility and high false negative rate. Of note is that the authors also considered T1 tumors in their series, as recently suggested by Leijte et al. (4), as a risk of metastasis should be considered for these patients.

Finally, we agree with the authors when they state that DSNB procedure is difficult to master and it should be performed in centers with a minimum number of cases. We look forward to have the results from the same group of investigators after the introduction of the complete DSNB technique in their clinical practice as this should minimize false negative rates and optimize its diagnostic accuracy. In order to achieve this goal, a recent report by the group with the most extensive experience worldwide highlight some modifications to the original DSNB technique: fine needle aspiration cytology before lymphoscintigraphy; serial sectioning when analyzing the nodes; intraoperative palpation after injection of patent blue and surgical exploration in case of non-visualized groin (4). Further clinical research in this area is needed to better define the place of the sentinel node biopsy in the management of penile cancer patients. In this respect a very interesting approach has been proposed by Tobias-Machado et al, who presented their encouraging results on 10 patients submitted to video endoscopic inguinal lymphadenectomy (5).

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Dr. Riccardo Autorino
Clinica Urologica, AOU Policlinico
Seconda Università
Napoli, Italy
E-mail: ricautor@tin.it

Dr. Sisto Perdonà
UO Urologia, Istituto Nazionale Tumori
Fondazione G. Pascale
Napoli, Italy

Case Report
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Mannitol Extravasation during Partial Nephrectomy Leading to Forearm Compartment Syndrome

Bradley A. Erickson, Ronald L. Yap, Joseph F. Pazona, Brian J. Hartigan, Norm D. Smith

Departments of Urology and Orthopaedics, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

ABSTRACT

We present the first known complication of forearm compartment syndrome after mannitol infusion during partial nephrectomy. We stress the importance of excellent intravenous catheter access and constant visual monitoring of the intravenous catheter site during and after mannitol infusion as ways to prevent this complication. Prompt recognition of compartment syndrome with appropriate intervention can prevent long-term sequelae.

Key words*: carcinoma, renal cell; nephrectomy; mannitol; compartment syndrome*
Int Braz J Urol. 2007; 33: 68-71

INTRODUCTION

Surgeons commonly use mannitol for partial nephrectomies that entail renal hilar clamping. We report a case of mannitol extravasation during a partial nephrectomy that led to forearm compartment syndrome requiring emergent fasciotomies.

CASE REPORT

A 36-year-old female underwent open partial nephrectomy for an incidentally found, enhancing 2.5 cm left lower pole mass (Figure-1). The patient had a medical history significant for IV drug abuse, hypertension and asthma. In the preoperative holding area, the anesthesia team noted that intravenous access was extremely difficult to obtain; this was thought to be secondary to the patient's prior IV drug abuse. The team made multiple attempts at IV access before ultimately placing two large bore (16G) peripheral IVs, both of which were used for infusion for the case duration.

The procedure proceeded without complications, with a cold ischemia time of approximately 30 minutes and a total OR time of 3.5 hours. Per usual for this type of case, we infused 12.5 grams of mannitol 5 minutes before hilar occlusion and 5 minutes after removing the clamps through the right peripheral forearm IV.

Postoperatively, the patient remained intubated because of a recent episode of asthma exacerbation and high airway pressures encountered during the case. Approximately 1 hour after arriving in the intensive care unit, the nurse noted that the patient's right hand was flexed in a "claw shape". In addition, her forearm was extremely tense, and the right forearm IV used for mannitol infusion was not working (Figure 2A and B). Because the patient was still intubated and sedated, she did not show signs of distress or complain of pain in the arm, but distal pulses and capillary refill were absent. An emergent

Figure 1 – *CT scan showing enhancing 2.5 cm lower pole mass.*

hand surgery consult was obtained and forearm compartment pressures were found to be > 120 mmHg (normal < 30 mmHg). The patient was emergently brought to the operating room by the hand surgery team where fasciotomies were performed. The compartment syndrome was later felt to be secondary to mannitol extravasation from the right forearm peripheral IV.

Fasciotomies were closed 7 days later when the swelling had diminished sufficiently. At two-month follow-up, the patient displayed no residual forearm or hand weakness and fasciotomy incisions were well-healed. Final pathology of the partial nephrectomy specimen showed a 2.5 cm grade-I clear cell renal cell carcinoma with negative margins.

COMMENTS

Intravenous infusions of mannitol expand intravascular volume and decrease cellular edema by minimizing the large intracellular fluid shifts that normally occur during periods of organ ischemia. Researchers theorize that a reduction in cellular edema more promptly restores blood flow to the ischemic organ after the insult is removed, as the vessels do not collapse from the surrounding engorged cells (1). These properties make it a useful renoprotective agent during partial nephrectomies.

Though mannitol itself is a relatively benign substance, its potent osmotic properties can be detrimental when it has extravasated into a closed space. For every 50 g of mannitol infused, a 1L intracellular to extracellular fluid shift is expected to occur (2). This fluid shift is easily accommodated intravascularly, but the relatively small forearm compartment is not as forgiving.

Compartment syndrome develops when interstitial pressures of a given muscular compartment

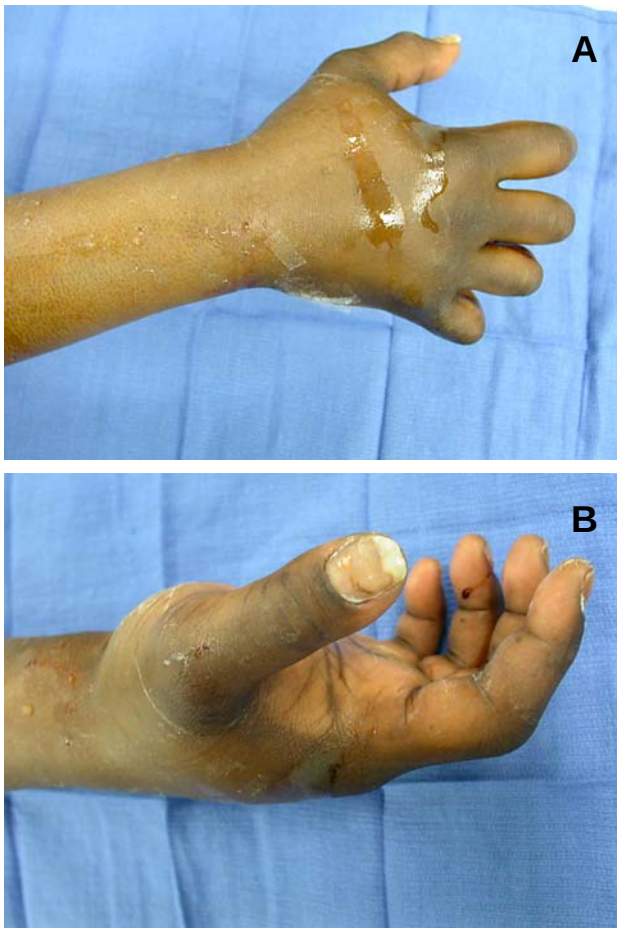

Figure 2A and B – *Elevated forearm compartment pressures lead to this typical flexed appearance.*

surpass those of the capillary perfusion pressures. When this occurs, the capillaries collapse, resulting in local hypoxia and eventual necrosis of the intercompartmental musculature. Common causes include bone fractures, extensive soft tissue injuries, reperfusion of ischemic tissue, high pressure and hypertonic intravenous fluid administration and medication extravasation (3). In this particular case, mannitol extravasation likely led to a large volume shift from the vascular space to the interstitium, critically raising compartmental pressures.

Mannitol extravasation leading to forearm compartment syndrome has been reported before (3-5) but not during partial nephrectomy. Many things about this case make it unique. First, as previously noted, obtaining IV access was difficult, and though two large bore IVs were ultimately placed, the venous integrity in a patient with a long-standing IV drug abuse history and who experienced multiple failed peripheral IV sticks prior to surgery could have been questioned. Though intravenous infusion through the right forearm IV remained constant throughout the case, small injuries to the proximal vasculature probably allowed for seepage of the mannitol into the interstitium. The phenomenon resembles the high incidence of IV infiltration observed in patients with long hospital stays requiring multiple venous punctures. Second, the fact that anesthesiologists usually obtain intravenous access prior to the positioning of the patient for partial nephrectomy can make it quite difficult to monitor the site during the case. When patients are put in a modified flank position, as often required for partial nephrectomy, surgeons must secure the arm to the armboards in order to help stabilize the patient. Placing the IV site without regard to the eventual location of the arm can often render the IV site inaccessible. Though this particular IV site was visible, it was not immediately accessible to the anesthesia team. It remains unclear whether the inability to continually monitor the IV site contributed to the eventual complication; however, had we diagnosed problems with the IV sooner, we might have infused mannitol at an alternate location. Finally, unconscious patients run a particular risk for extravasation injury (3). The 4 Ps of compartment syndrome (pain, paresthesia, pallor, pulselessness) are difficult to monitor without patient feedback and the diagnosis must be made by observation of the IV site alone. Constant monitoring of the IV site is, therefore, of utmost importance in unconscious patients. Early recognition by the intensive care nurse undoubtedly bears responsibility for preserving the underlying musculature in this patient.

Though this unfortunate case did not prompt us to abandon our use of mannitol during partial nephrectomies, we did adopt some new practices with the goal of preventing a repeat of this complication. First, if venous integrity seems questionable, we ask that mannitol be infused through a central venous catheter. This requires communication with the anesthesia team early in the procedure and again before infusion of mannitol. Second, we ensure that the IV site intended for mannitol instillation remains visible to the anesthesia team throughout the case. Though this sometimes requires creative positioning and IV placement, none of these minor adjustments have compromised any parts of our subsequent cases. Finally, in unconscious patients, we stress monitoring of the peripheral IV site and surrounding soft tissue to all involved in postoperative care, as it is unclear over what time period compartment syndrome occurs (In this particular case, the nurse noticed symptoms approximately 3 hours after instillation).

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Bradley A Erickson
Dept Urology, Feinberg Sch Medicine
Northwestern University, Tarry Building #16-703
303 East Chicago Avenue
Chicago, IL, 60611, USA
Fax: + 1 312 908-7275
E-mail: b-erickson@md.northwestern.edu

EDITORIAL COMMENT

Compartment syndrome is a rare but well known complication observed in trauma patients or may be due to incorrect positioning of patients during surgery. In urology, it may occur after time consuming procedures performed in lithotomy position (like radical prostatectomy or cystectomy) and is usually localized in the lower legs. Compartment syndrome of the forearm due to infusion of various medications is described as a rare phenomenon in the literature, as the authors pointed out.

Even if this particular complication is rather an anesthesiological pitfall than a urological complication this case is remarkable, because the use of mannitol is common in renal surgery, especially in partial nephrectomy or kidney transplantation. In the described case, the awareness of the personnel led to an early recognition of the complication and an immediate successful intervention.

Two facts are noteworthy in this case. There is no doubt about the indication for mannitol infusion with nephroprotective goals during partial nephrectomy. However, considering the problems of the intravenous access, caused by the patient's history of IV drug abuse, the attention should have been directed to the risk earlier and precautions should have been taken. I agree with the authors, that in this case a central venous access would have been suitable to avoid further complications. General anesthesia for partial nephrectomy, especially when there is a significant risk of major bleeding, as in the present case, should never been managed with a peripheral venous access alone. A central venous access should always be the first choice in terms of patient's safety.

Dr. Andreas H. Wille
Department of Urology
University Hospital Charite, Campus Mitte
Humboldt-University Berlin
Berlin, Germany
E-mail: andreas.wille@charite.de

Case Report
International Braz J Urol Vol. 33 (1): 72-73, January - February, 2007

True Hermaphroditism presenting as an Inguinal Hernia

Kadir Ceylan, Ekrem Algun, Mustafa Gunes, Hasan Gonulalan

Yuzuncu Yil University, Faculty of Medicine, Departments of Urology and Endocrinology, Van, Turkey

ABSTRACT

A 21-year-old patient with cryptorchidism was found to have a left inguinal mass on physical examination. The patient was operated with a diagnosis of bilateral cryptorchidism and left inguinal hernia. Besides bilateral inguinal undescended testicles, female genital organs like fallopian tubes, uterus and ovary were found on the exploration.

Key words*: cryptorchidism; inguinal hernia; urogenital abnormalities; true hermaphroditism*
Int Braz J Urol. 2007; 33: 72-3

INTRODUCTION

In true hermaphroditism, both ovarian and testicular tissues are present in one or both gonads. Differentiation of the internal and external genitalia is highly variable. The external genitalia may simulate those of a male or female, but most often, they are ambiguous (1). The incidence is unknown, but more than 400 cases have been reported to this date. To justify the diagnosis, there must be histological documentation of both types of gonadal epithelium (2). The condition is usually diagnosed in the first few years of life (3). Here, we report a patient who first presented with bilateral cryptorchidism and left inguinal hernia when he was 21 years old.

CASE REPORT

A 21-year-old male patient presented with bilateral cryptorchidism and a mass in the left inguinal canal. He had a male phenotype with fully developed secondary sex characteristics. There were no hypospadias, gynecomastia or any other somatic anomaly. He presented normal morning erection and ejaculation and no history of urethral bleeding. Testes were palpable on physical examination in the inguinal canal. Ultrasound examination revealed bilateral cryptorchidism and left inguinal hernia. Serum testosterone, LH and FSH levels were within normal limits for an adult male and he had azoospermia on semen analysis. He was operated with a diagnosis of bilateral cryptorchidism and left inguinal hernia. On inguinal exploration bilateral cryptorchidism and uterus were found as well as fallopian tubes and ovary on the left inguinal canal. Thus, there were 3 separate gonads: one testis in the right side and one testis plus one ovary in the left side. Right testis orchiopexy was performed. Left testis and the female genital duct remnants were excised (Figure-1). Pathological examination of the testicular specimen revealed germinal aplasia of the testicular tissue. Unfortunately, karyotype analysis could not be performed for technical insufficiency.

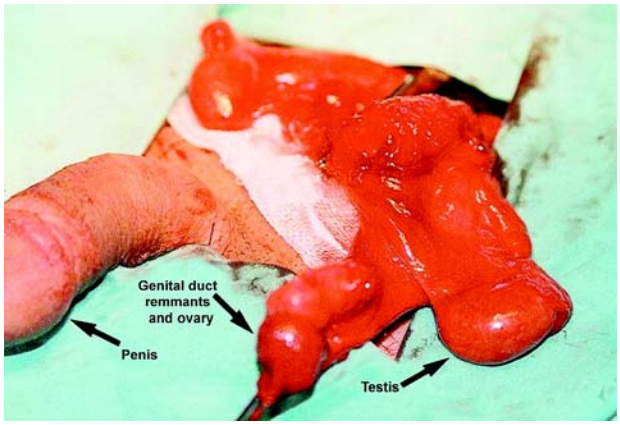

Figure 1 – *Intraoperative view of the female genital duct remnants, ovary and testis.*

COMMENTS

True hermaphroditism is a phenotypically and genetically an heterogeneous condition. Gonadal tissue may be located at any level along the route of embryonic testicular descent and is frequently associated with an inguinal hernia. There may be unilateral or bilateral ovotestis or a testis on one side and ovary on the other side. A uterus is usually present, though it may be hypoplastic or unicornous (1-4). Our case had testis on the right side and a testis and female genital structures on the left side. Ovarian tissue was dysgenetic and testicular tissue showed germinal aplasia.

In true hermaphroditism, the degree of virilisation of the external genitalia depends on the capacity of testicular tissue to secrete testosterone and the presence or absence of a uterus and tubes. Although approximately 70% of true hermaphrodites are raised as males, less than 10% have normal male external genitalia (1,2). Our case had completely normal external genitalia except for cryptorchidism, moreover, the patient had fully developed secondary sexual characteristics and defined erections and ejaculations.

Most of the true hermaphrodites have ambiguous genitalia and are diagnosed in the first few months to years of their life (3). Our case is unique because there is no diagnosis during the first 21 years of his life.

True hermaphroditism should also be considered in the differential diagnosis of cryptorchidism and inguinal hernia in a patient in the second or third decade.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Kadir Ceylan
Yüzüncü Yil Universitesi
Tip Fakültesi
Uroloji Anabilim Dali
Van, Turkey
E-mail: drceylan26@yahoo.com

Case Report
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Bovine Pericardium In Penile Prosthesis Reimplantation

Eduardo J. Lopes, Tarsila C. Santos, Modesto Jacobino

Section of Urology, University Hospital, Federal University of Bahia, Salvador, Bahia, Brazil

ABSTRACT

We present a case of a patient who underwent a late penile prosthesis implant using bovine pericardium as a complement to the tunica albuginea involved in intense fibrosis that destroyed the corpus cavernosum after an infectious manifestation. The advantages of using bovine pericardium in the substitution of the tunica albuginea are discussed and its first use as a penile prosthesis lining is reported.

Key words*: penile prosthesis; infection; graft; pericardium; cattle*
Int Braz J Urol. 2007; 33: 74-6

INTRODUCTION

The incidence of infection in penile prosthesis implant surgery is approximately 3% (1,2). With this low percentage, the late implant is the most adopted option, and, eventually, the intense fibrosis that involves the corpora cavernosa makes the re-implantation of a new prosthesis more difficult (1,2).

The authors report a case of a diabetic patient who presented extrusion of the prosthesis through the gland. Conservative treatment was initially adopted, followed by a late implant that required a reconstruction of the tunica albuginea with biological material.

CASE REPORT

A 62-year-old diabetic patient with a penile prosthesis implant presenting a perforation of the gland and partial extrusion of the prosthesis that had been implanted 3 years before was attended in emergency. As the right unit of the prosthesis perforated the gland and was partially extruded, its removal was achieved through the extrusion location. The left unit was removed through the same orifice after verification that both units were occupying the same space due to a complete destruction of the intercavernous septum. The material was collected for culture and antibiotic therapy with cephalosporin and aminoglycoside was begun. Following this, the space was cleansed with 0.9 % physiological saline containing gentamicin. A suture of the corpus cavernosum was performed using vycril 2-0 and the orifice of the glandar corpus spongiosum was sutured with chrome-catgut 3-0 in 2 simple stitches. The result of the culture revealed the presence of Staphylococcus aureus and Streptococus epidermidis sensitive to the adopted antibiotic therapy.

Sixty days after the resolution of the infectious condition, a new AMS 650 prosthesis was reimplanted through penoscrotal access. The prophylactic antibiotics used were cefazolin (1g/IM/day for 72 h), gentamicin sulfate (80 mg/IM, 8 every 8 hours

for 48 h), metronidazol (400 mg IV of 8 every 8 h for 48 h), and gentamicin sulfate (160 mg in physiological saline solution) where the prosthesis was submersed. Due to the intense fibrosis and the small space within the tunica albuginea, it was only possible to implant a single unit. We opted for the inverted insertion of the prosthesis in the distal extremity of the tunica albuginea using the small space inside the corpus cavernosum (Figures-1 and 2). The 4 mm bovine pericardium was used to line the entire extension of the implanted prosthesis, complementing the fibrosed tunica albuginea (Figure-3). Two years later, the patient is satisfied with the result and has been maintaining regular sexual relations without any complaints or recurrences.

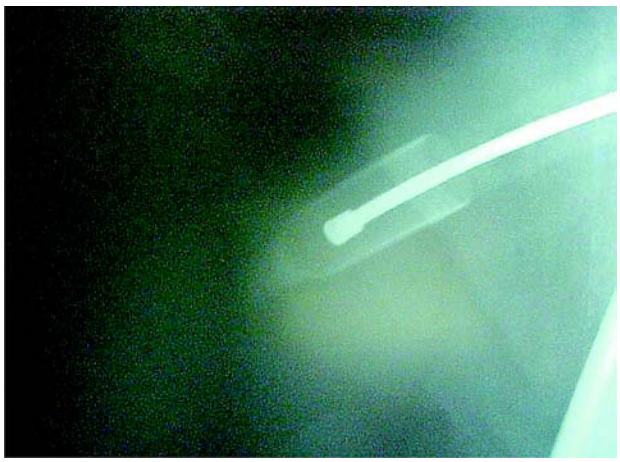

Figure 1 – *Rx showing a single prosthesis implanted in an inverted fashion.*

Figure 2 – *AMS 650 prosthesis with the inferior extremity inserted in the gland.*

Figure 3 – *Aspect of the prosthesis lined with the bovine pericardium.*

COMMENTS

When infection occurs in a penile prosthesis implant, 2 procedures can be adopted: 1) a rescue procedure, which requires an exhaustive cleansing of the area, antibiotic therapy and the re-implantation of a new prosthesis at the same time (this is considered an exception despite the good result obtained by some authors (2); and 2) late implant, necessitating removal of the prosthesis, local cleansing, specific treatment for the infection and implant of a new prosthesis following remission of the infection (2).

We chose the second option because of our greater experience with it and because this procedure is more discussed and accepted. The period between the removal of the prosthesis and the re-implant remains uncertain, varying from 2 to 39 months (with a mean of 8 months) (1,2). In this case, we opted for the implant of a new prosthesis 2 months after the first intervention.

Even though synthetic materials are available and inactive, they have the disadvantage of presenting a larger rate of infection, inelasticity and fibrosis of the corpora cavernosa (1,2). On the other hand, the tensional strength of the biological material has been questioned, this material is not readily available and has a larger risk of diseases transmission (1).

We have chosen bovine pericardium because of its lower cost, inertia, elasticity, absence of transmission of diseases, low probability of retraction and good resistance to tension that allow it to cover large defects without forming protuberances (3). Despite having never been used as a lining for a penile prosthesis, we believe that it is another option in extreme situations such as the one we are describing.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Eduardo José Andrade Lopes
Rua Altino Serberto de Barros, 241 / 405
Ed. Memorial Itaigara
Salvador, BA, 41850-010, Brazil
Fax: + 55 71 3351-7424
E-mail: ejalopes@terra.com.br

Case Report
International Braz J Urol Vol. 33 (1): 77-79, January - February, 2007

Painless Inter Epididymal Testicular Torsion of the Spermatic Cord

Salomon V. Romano, Haime S. Hernan, Norberto Fredotovich

Section of Urology, Hospital Durand, Buenos Aires, Argentina

ABSTRACT

Inter epididymal testicular torsion of the spermatic cord is extremely rare and usually diagnosed at surgery. We present an unusual case of spermatic cord torsion in a 14-year-old male patient. It is important to highlight that the torsion occurred only on the distal half of the epididymis leaving the head untwisted and edematous. In addition, the fact that this condition was painless made this case extremely rare and motivated our presentation.

***Key words**: testis; epididymis; torsion*
Int Braz J Urol. 2007; 33: 77-9

INTRODUCTION

Testicular torsion is considered a surgical emergency. The testis present irreversible damage if the torsion is not resolved within the first 6 hours. Torsion usually occurs in young pre-puberty males, between 12 and 18 years old, (1) even though it can be seen in other ages. The prevalence is estimated to be 1 in 4000 patients under 25 years old.

The inter epididymal torsion of the spermatic cord is one of the most infrequent situations. In our patient it occurred due to the abnormal insertion between the epididymis and the testicle. This kind of torsion is clinically undistinguishable from the typical spermatic cord torsion and the diagnosis can only be made during surgical exploration.

It is well known that spermatic cord torsion is associated with intense pain. In this particular case, it was painless**.**

CASE REPORT

A fourteen-year-old male patient was first seen at the urology section due to a painless growth of his left scrotum, beginning one month before his visit. No history of trauma or masturbation habit was refereed, but a similar episode took place 2 years before, with complete remission after medical treatment.

Previous evaluation in another center with ultrasonography (US) and tumor markers assumed its etiology as inflammatory and as a consequence treated the condition with ice, antibiotics and oral analgesics.

At physical examination, an increased volume and high consistence on left testicle was found, but the patient said the size was half of what it was initially, without spontaneous or induced pain.

The US showed a homogeneous round left testicle, without tumor, with a para-testicular solid

16 x 21 mm hypoechoic mass with small hydrocele (Figure-1).

Blood flow was normal according to a color Doppler ultrasonography. Contralateral (right) testis and epididymis were normal.

The left testicle was explored using the inguinal approach, showing a partial intravaginal 360-degrees inter epididymal testicular torsion of spermatic cord. The torsion site was in the epididymal corpus, leaving the head in place (Figure-2), corresponding to the hypoechoic mass described previously. The necrotic aspect of the testicle motivated the orchiectomy. In the pathological study, a hemorrhagic infarction was confirmed.

The right testicle was surgically explored using the scrotal approach. We found a low insertion of the epididymis in relation to the testicle, and orchiopexy was performed.

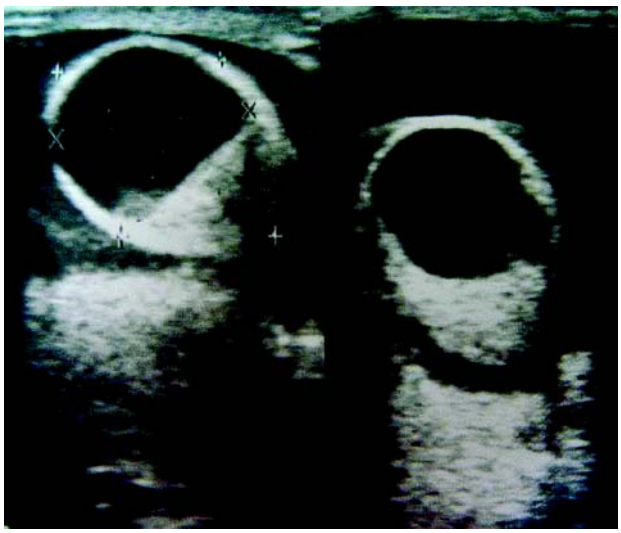

Figure 1 – *Paratesticular solid hypoechoic mass.*

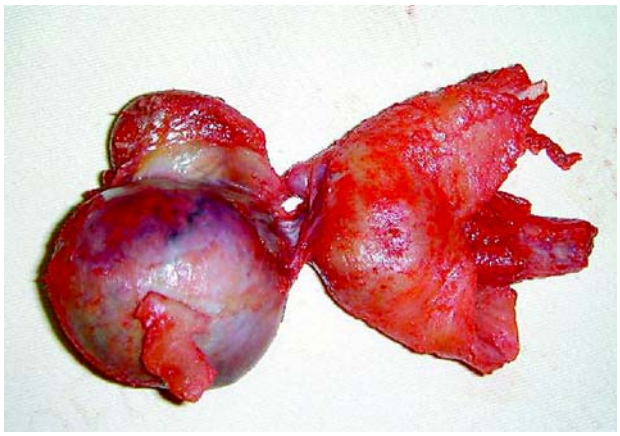

Figure 2 – *Torsion in the epididymis corpus, leaving the head in place.*

COMMENTS

Two types of spermatic cord torsion are described in literature. In the extravaginal torsion, the testicle and the vaginal sac turn over the spermatic cord at the external inguinal ring, due to a lack of adherence of the tunica vaginalis to the scrotal wall. This type of rotation can only be seen in fetus and neonates (2). In the intravaginal torsion, there is a previous anatomic defect. The high and narrow insertion of the tunica vaginalis in the testicle allows it to remain free in the vaginal sac as a "bell clapper". This kind of defect would be bilateral and would justify preventive orchiopexy in the contralateral testis (3). Another type of intravaginal torsion is between the testis and the epididymis. This rare presentation is reported only in disjunction between testis and epididymis (4). In this type of anatomic defect, isolated epididymis torsion has been reported. Also, torsion of the testicular and epididymal appendages can occur. These structures can turn over their own axis and produce pain and local inflammation, mimicking the clinical presentation of spermatic cord torsion (3).

In the present case, the unusual presentation with hardness and painless testicle in a young male patient, together with unspecific complementary studies, lead us to think it was a testicular cancer and therefore, an inguinal approach was performed.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Salomon Victor Romano
25 de mayo 846
Vicente Lopez, BA, 1638, Argentina
Fax: + 54 11 4791-6735
E-mail: sromano1@arnet.com.ar

EDITORIAL COMMENT

The case-report herein describes an anecdotal situation of painless testicular torsion of the spermatic cord in an unusual location. The reader should bear in mind the rarity of this clinical event. On the other hand, the subject raised allows the editor to draw some reflections about this still controversial issue of acute scrotum. The main differential diagnosis of the acute scrotum includes testicular torsion and inflammatory conditions. Color Doppler ultrasound is the current imaging modality of choice for the radiological evaluation of acute scrotum, replacing other methods such as nuclear scintigraphy, Doppler flowmetry and gray scale ultrasound. Unfortunately, we cannot always rely on the exam. Bentley et al. discussed variations in degrees of bell clapper deformity and its influence in attachments of tunica vaginalis representing possibility of testicular blood flow despite spermatic cord torsion (1). In their series, 4 of 14 cases had testicular torsion confirmed intraoperatively despite a normal color Doppler ultrasound. One should also remember that ultrasound is an operator dependent test and a false-negative report may end catastrophically.

A more appealing and rational algorithm for the management of acute scrotum is also discussed in the paper of Bentley et al (1). In case of obvious suspicion of testicular cord torsion, surgical operation is mandatory. When there is a low index of suspicion, one should perform color Doppler ultrasound and the diagnosis of inflammation is acceptable only in case of increased flow, while patients with "normal flow" should be also operated. We agree with others that 6 hours is the desirable time form the beginning of the onset of pain to have the case resolved.

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Dr. Antonio Macedo Jr.
Division of Urology
Federal University of São Paulo, UNIFESP
São Paulo, SP, Brazil
E-mail: amcdjr@uol.com.br

International Braz J Urol Vol. 33 (1): 80-86, January - February, 2007

Increased Urinary N-acetyl-beta-D-glucosaminidase Activity in Children with Hydronephrosis

Sylva Skalova, Pavel Rejtar, Stepan Kutilek

Departments of Pediatrics and Radiology, Charles University in Prague, Faculty of Medicine in Hradec Kralove, Czech Republic, and Center for Clinical and Basic Research, Pardubice, Czech Republic

ABSTRACT

Objective: Hydronephrosis leads to deterioration of renal function. As urinary N-acetyl-beta-D-glucosaminidase (U-NAG) activity is considered a sensitive marker of renal tubular impairment, our aim was to measure U-NAG in children with hydronephrosis and to look for a relationship among selected clinical parameters.
Materials and Methods: We studied 31 children (22 boys and 9 girls, mean age 2.3 ± 2.5 years) with hydronephrosis grade 1-4 that had U-NAG/creatinine ratio (U-NAG/Cr) measured.
Results: The U-NAG/Cr was significantly higher in patients with hydronephrosis compared to reference data ($p = 0.002$). There was no difference in U-NAG/Cr between children with unilateral and bilateral hydronephrosis ($p = 0.51$). There was no significant difference in U-NAG/Cr between children with grades 1-3 (pooled data) and grade 4, respectively ($p = 0.89$). There was no correlation between U-NAG/Cr and the grade of hydronephrosis ($r = 0.01$).
Conclusions: U-NAG/Cr is increased in children with hydronephrosis grade 1-4, and there is no relationship with the grade of hydronephrosis. U-NAG is a useful marker of renal tubular dysfunction, however its relationship with the degree of kidney damage in patients with hydronephrosis should be considered as doubtful.

Key words*: children; hydronephrosis; N acetyl beta d glucosaminidase*
Int Braz J Urol. 2007; 33: 80-6

INTRODUCTION

Hydronephrosis leads to deterioration of renal function (1,2). N-acetyl-beta-D-glucosaminidase (NAG) is a lysosomal enzyme, which is abundantly present in the cells of the proximal tubule and is considered as a very sensitive marker of renal tubular impairment in various disease states (3,4). Our aim was to measure urinary NAG activity (U-NAG) in children with hydronephrosis and to look for a possible relationship between patients´ clinical data and U-NAG.

MATERIALS AND METHODS

We studied 31 children (22 boys and 9 girls, mean age 2.25 ± 2.50 years; range 0.08 - 9.08 y) with hydronephrosis. Informed consent was obtained from parents of each patient prior to any procedures described in this paper. Hydronephrosis was diagnosed by means of abdominal ultrasonography either prenatally (n = 20) or postnatally (n = 11), the latter at the mean age of 6 ± 14 months (range 0.1 - 48 months). In all patients, the hydronephrosis and its grade was further evaluated postnatally by means of ultrasound

and ^{99m}Tc mercaptoacetyltriglycine (MAG3) "well tempered" renography (5,6). Hydronephrosis was graded according to the Society for Fetal Urology (SFU) classification (1). Vesicoureteral reflux was ruled out in all patients by voiding cystourethrography. None of the patients had solitary kidney.

In 18 patients the hydronephrosis was unilateral, grade 1-4 (mean 3.1 ± 0.8), and in 13 patients, the hydronephrosis was bilateral, grade 1-4 (mean 2.9 ± 0.7). In the patients with bilateral hydronephrosis and different grade on each side, the highest grade was taken into consideration. Therefore, the diagnostic distribution was as follows: grade 1, n = 1; grade 2, n = 2; grade 3, n = 16; grade 4, n = 12. All patients had their kidney functions evaluated by the "well-tempered" diuretic renogram with ^{99m}Tc MAG3 (5-7). The relative renal function, expressed as percentage represented by the contribution of each kidney to the global renal function was evaluated. In only 2 children with unilateral hydronephrosis, the relative function of the affected kidney was 35%. In the remaining 17 children with unilateral hydronephrosis, the relative function of the affected kidney exceeded 40%. The mean value of the relative function of the affected kidney in the 19 patients with unilateral hydronephrosis was 47.3%. In the entire group of 31 children, the mean relative renal function of the right and left kidney was 50.4%: 49.6%. In patients with hydronephrosis grade 1-3 there were no signs of obstruction, while obstruction was present in patients with grade 4. The obstruction was evidenced by several criteria, such as progressive dilatation of the calyces and pelvis on ultrasound imaging; > 5% decrease per year in the function of hydronephrotic kidney on ^{99m}Tc MAG3 renogram; obstructive pattern of renogram curve after administration of furosemide with a clearance half-life greater than 20 minutes (5-7).

None of the patients underwent any surgical procedure due to hydronephrosis prior to the U-NAG measurements. Patients with grade 4 were later confined to surgical treatment.

All patients had their U-NAG and serum and urinary concentrations of creatinine (S-Cr, U-Cr) evaluated. None of the patients suffered from pyelonephritis at the time of the U-NAG/Cr and S-Cr evaluation. All patients were free from infection at least 4 months prior to the U-NAG/Cr and S-Cr evaluation. Urinary NAG was evaluated in the spot urine, collected after the first morning void. The blood and spot urine were collected either at the time of the ultrasonographic examination or in a period of ± 1 month within abdominal ultrasonography and ^{99m}Tc MAG3 renography. The influence of endogenous enzyme inhibitors was eliminated by diluting the urine specimens' 20-fold. The urinary catalytic activity of NAG was then determined by fluorimetric assay. The S-Cr and U-Cr were estimated by Jaffe's kinetic method on Modular Analyser (Roche Diagnostics GmbH, Mannheim, Germany). The S-Cr values were expressed in μmol/L. The U-NAG values were expressed as the urinary NAG/creatinine (U-NAG/Cr) ratio in nkat/L : mmol/L. To eliminate the influence of age, the obtained results of S-Cr and U-NAG/Cr were expressed as standard deviation scores (SDS) or Z-scores by the equation SDS = (actual individual value - mean value for age) /standard deviation for age with the use of age-related laboratory reference data for S-Cr and previously obtained reference data for U-NAG/Cr (4). These reference standards of U-NAG/Cr were obtained from a total of 262 children (aged 0-18 years), and in particular from 213 children aged 0-10 years (4). The obtained values were compared to the age-related reference data and correlated with grade of hydronephrosis. The presence of either unilateral or bilateral hydronephrosis was also taken into consideration.

The statistical analysis was performed by t-test. The linear regression analysis was performed to compare the relationship among respective parameters. For all results, a p-value < 0.05 was required for statistical significance.

RESULTS

The U-NAG/Cr values were significantly higher in the patients with hydronephrosis in comparison to the reference data (Table-1). There was no difference in U-NAG/Cr between children with unilateral and bilateral hydronephrosis (p = 0.51).

As there were low patient numbers with hydronephrosis grade 1-2, we pooled the U-NAG/Cr data for this group of children together with hydronephro-

***Table 1** – U-NAG/Cr and S-Cr values expressed as Z-scores ± SD.*

Parameter	Mean	SD	p Value †
U-NAG/Cr (grade 1-4)	4.92	5.38	0.002
U-NAG/Cr (grade 1-3)	5.02	5.29	0.0006
U-NAG/Cr (grade 4)	4.76	5.74	0.015
S-Cr (grade 1-4)	0.53	1.09	0.05

U-NAG/Cr (grade 1-4), data from patients with hydronephrosis grade 1-4 (n = 31); U-NAG/Cr (grade 1-3), pooled data from patients with grade 1-3 (n = 19); U-NAG/Cr (grade 4), data from patients with grade 4 (n = 12); S-Cr (grade 1-4), data from patients with hydronephrosis grade 1-4; † compared to reference data.

sis grade 3. When compared to reference data, patients with grade 1-3 (n = 19) and those with grade 4 (n = 12) had significantly higher U-NAG/Cr activity (Table-1). However there was no significant difference in U-NAG/Cr between children with grade 1-3 and grade 4, respectively (p = 0.89). Neither was there any significant difference in the U-NAG/Cr values between children with unilateral and bilateral hydronephrosis when stratified for grade (grade 1-3 and 4, respectively; p = 0.55 and p = 0.50, respectively). The S-Cr was within ± 2 SD range in 30/31 patients, however this was still significantly higher in comparison to reference data (Table-1). There was no difference in S-Cr between children with unilateral and bilateral hydronephrosis (p = 0.82). No correlations were observed between U-NAG/Cr and the grade of hydronephrosis (r = 0.01), or between S-Cr and the grade of hydronephrosis (r = -0.07). We found a positive correlation between U-NAG/Cr and S-Cr, which reached statistical significance (r = 0.40, p = 0.05).

COMMENTS

The high values of U-NAG/Cr in our patients with hydronephrosis suggest renal tubular impairment and are in accordance with previously reported results, which are only scarce (8-13). Experimental studies revealed high U-NAG in rats with partial ureteral obstruction and hydronephrotic atrophy (8,9). Increased U-NAG was detected in urine obtained from renal pelvis (10,11) and bladder (11), with pelvic U-NAG levels higher than bladder U-NAG levels (11) in children with unilateral hydronephrosis. High U-NAG/Cr levels were observed in children with renal pyelectasis (12). Interestingly, post-operative increase in U-NAG levels was reported in patients with hydronephrosis (13).

In our patients, the U-NAG/Cr values, measured in the spontaneously voided urine, were increased, regardless whether there was unilateral or bilateral hydronephrosis. Previously published observations based on evaluation of isotope renal function and imaging procedures gave evidence that children with grade 4, and some with grade 3 of hydronephrosis, have impaired renal functions and should be confined to surgical treatment, which has been proven as beneficial (1,2,14,15). It was therefore of particular interest to see if U-NAG was somehow related to the grade of hydronephrosis. However, the high levels of U-NAG did not correspond to the ultrasonographic degree of renal damage, as there was no correlation between U-NAG and the grade of hydronephrosis, and there was no difference in U-NAG between grades 1-3 and 4, respectively. Similarly, the renal functions, as assessed by the ^{99m}Tc MAG3 renography, were not severely impaired. There was no difference in U-NAG/Cr between children with unilateral and bilateral hydronephrosis. These results might suggest that the renal function, as assessed by ^{99m}Tc MAG3 renography might not be solely related to the grade of hydronephrosis, and that U-NAG in hydronephrosis does not depend on the amount of affected renal tissue. Furthermore, we cannot rule out that the U-NAG can reflect even very mild changes in renal tubular function, which might occur even in low-grade non-obstructive hydronephrosis. There was a mild elevation of S-Cr, which reached statistical significance, and there was also a mild correlation between U-NAG/Cr and S-Cr. However, the changes in S-Cr in our group of patients are strongly obscured by the fact that all but one S-Cr values remained within the ± 2 SD range and that there was no difference between unilateral and bilateral hydronephrosis.

In conclusion, U-NAG/Cr is increased in children with hydronephrosis grade 1-4, however, there is no relationship with the grade of hydronephrosis or with the amount of affected renal tissue. U-NAG/

Cr is a useful marker of renal tubular impairment, however its relationship with the degree of kidney damage in patients with hydronephrosis should be considered as doubtful.

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Prof. V. Palicka and his team from the Institute of Clinical Biochemistry and Diagnosis at the Faculty of Medicine in Hradec Králové performed the S-Cr and U-NAG/Cr analyses.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Sylva Skálová
Department of Pediatrics
Charles University in Prague
Faculty of Medicine in Hradec Králové
Czech Republic
Fax: + 420 49583-2030
E-mail: skalova.s@seznam.cz

EDITORIAL COMMENT

Congenital obstructive nephropathy represents a major cause of renal insufficiency in infants and children. At present, two puzzling issues of congenital hydronephrosis still need to be elucidated. One is the diagnosis of obstruction (distinguishing an obstructed from a nonobstructed collecting system), and the other is the existence and definition of a no-return point of renal damage. It is our aim to find a urinary biomarker aids in the diagnosis of renal tubular damage and medical therapy is given to protect renal function and accelerate its recovery after intervention.

NAG excretion in urine is widely used as a marker of tubular and glomerular injury in differential pathological states in human diseases. The authors measured urinary NAG in children with hydronephrosis and assert increased U-NAG/Cr in children with hydronephrosis grade 1-4 (although there were no signs of obstruction in patients with hydronephrosis grade 1-3), but there is no relationship with the grade of hydronephrosis. The increase of U-NAG in children with unobstructed renal pyelectasis raise a question that if there is renal damage in children only with renal pyelectasis. A recent paper which showed significant discordance between conventional imaging and histological findings in congenital ureteropelvic junction obstruction perhaps could answer this question (1). However, it also needs long-term follow up to see if the children with unobstructed obstruction have the risk for progressive renal damage. It is exciting if a prognostic factor indicating renal damage in children with congenital hydronephrosis can be confirmed by subsequent studies. More thoughtful work is needed to make this a reality.

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Dr. Y. Yang
Department of Pediatric Surgery
China Medical University
Shenyang City, China
E-mail: yangxy70@hotmail.com

EDITORIAL COMMENT

The authors investigated the urinary secretion of N-acetyl-beta-D-glucosaminidase (U-NAG) in the patients with unilateral and bilateral hydronephrosis in order to look at the relation between the severity of the U-NAG secretion and the grade of hydronephrosis. They convincingly show that there is an increased secretion of U-NAG in children with hydronephrosis due to ureteropelvic junction (UPJ) obstruction reflecting proximal tubular injury in these patients. However, they failed to demonstrate the significant relation between the degree of hydronephrosis and renal damage and U-NAG secretion, therefore eliminating the utilization of this marker in the decision making process for surgery in patients with antenatal hydronephrosis. Most urologists manage the majority of the cases of fetal hydronephrosis due to UPJ obstruction by nonoperative observation, reserving surgery only for patients with deterioration of renal function or clinical symptoms. However the natural history of fetal hydronephrosis, the optimal time for surgery, the ability to define which kidney will benefit from surgical intervention, and which children will have deterioration in renal function while on surveillance, is still a matter of controversy. We have recently published our experience regarding predictive factors

for surgery in children with antenatal diagnosis of hydronephrosis, which led to postnatal diagnosis of UPJ (1). Society for Fetal Urology (SFU) grade 3-4 of postnatal hydronephrosis and relative renal function (RRF) less than 40% are significant independent predictive factors for surgery. Preservation of renal function is a main goal of follow up of a patient with antenatal hydronephrosis. Although conservative treatment of these patients may spare them unnecessary surgery, it always carries some risk of irreversible loss of renal function. The use of different tissue and urinary markers in the clinical setup allows the diagnosis of urinary obstruction at the early stage therefore avoiding renal parenchymal damage. Previous studies confirmed increased urinary secretion of transforming growth factor-β (TGF-β) and epidermal growth factor (EGF) in obstructive uropathy making them attractive markers for early diagnosis of renal parenchymal damage. However, the search for more sensitive markers is needed in order to confirm an obstruction at the earliest level and proceeding with the surgery in order to spare these patients unnecessary diagnostic examinations and avoiding irreversible renal damage. The authors should be congratulated for their efforts to find out a new predictive factor of renal function deterioration. Further studies are needed to elucidate a precise mechanism, which is leading to renal parenchymal damage in patients with UPJ obstruction, which could in turn help develop new diagnostic modalities.

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Dr. Boris Chertin
Department of Urology
Shaare Zedek Medical Center
Jerusalem, Israel
E-mail: bchertin@yahoo.com

EDITORIAL COMMENT

This study evaluated the utility of U-NAG/Cr as a marker for renal obstruction in patients with hydronephrosis. All patients had vesicoureteral reflux ruled out and underwent a well-tempered renogram which was interpreted with fairly strict obstructive criteria (diminished function or t1/2 > 20 min.). The study population included 16 patients with grade 3 hydronephrosis and 12 patients with grade 4 hydronephrosis. There were too few patients with grade 1 (n = 1) and grade 2 hydronephrosis (n = 2) to draw any valid conclusions for these groups. Patients U-NAG/Cr ratios were compared to historical reference controls.

Although U-NAG/Cr levels were elevated in all patients with hydronephrosis compared to the reference population, U-NAG/Cr did not distinguish between those with and without MAG-3 evidence of obstruction. Furthermore, U-NAG/Cr did not differentiate between those with grade 4 and those with lesser grades of hydronephrosis. In fact, grade 4 patients had lower mean UNAG/Cr (4.76) than those with grades 1-3 (5.02). They conclude that U-NAG/Cr is not likely to be a useful marker for significant renal obstruction.

The finding that U-NAG/Cr levels were elevated in all patients with hydronephrosis merits

further consideration. It implies that even small degrees of hydronephrosis may adversely affect tubular function beyond our capability to measure. Due to the small numbers of grades 1 and 2, these conclusions are best limited to grades 3 and 4. Future studies in patients with grades 1-2 hydronephrosis should be performed before concluding that U-NAG/Cr is elevated even with low grade hydronephrosis.

A number of questions were left unanswered. They imply that all patients with grade 4 hydronephrosis were obstructed and underwent surgery. In such patients, did U-NAG/Cr levels return to normal after repair? If so, then this would imply that NAG might be a potential marker for resolution of obstruction in patients with persistent hydronephrosis after repair. Was there a difference in U-NAG/Cr levels between those that presented later in life with symptoms and those detected prenatally? Lastly, there is no comment regarding the duration of follow-up in these patients. It is conceivable that a change in U-NAG/Cr over time may correlate with subsequent deterioration.

Unfortunately, we are still searching for the "holy grail" of hydronephrosis management — a highly sensitive, highly specific marker of functionally significant obstruction, which is detectable before radiographic obstruction/deterioration, or clinical symptoms develop.

Dr. David R. Vandersteen
Pediatric Urologic Surgeon &
Associate Chief of Surgery
Children's Hospitals and Clinics of Minnesota
Professor of Urology,
Mayo Graduate School of Medicine
Minneapolis, Minnesota, USA
E-mail: dvandersteen@pediatricsurgicalassociates.com

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Laparoscopic Upper-Pole Nephroureterectomy in Infants

Marcio L. Miranda, Antonio G. Oliveira-Filho, Patricia T. Carvalho, Elaine Ungersbock, Hugo Olimpio, Joaquim M. Bustorff-Silva

Division of Genitourinary Surgery, Pediatric Surgery Unit, State University of Campinas, Unicamp, Campinas, Sao Paulo, Brazil

ABSTRACT

Objective: Report the results of laparoscopic upper-pole nephroureterectomy in infants.
Materials and Methods: Six consecutive infants underwent 7 laparoscopic upper-pole nephroureterectomy. Pre and postoperative evaluation included renal sonography, voiding cystourethrogram and renal scintigraphy. All infants showed upper-pole exclusion. Surgery was performed through a transperitoneal approach with full flank position in all infants. Three or 4 ports were used according to the necessity of retracting the liver. The distal ureter was ligated close to the bladder whenever reflux was present and the dysplastic upper-pole was divided with the help of an electrocautery. Data regarding operative time, postoperative use of analgesics, time to resume oral feeding, hospital stay and tubular function were collected and analyzed.
Results: All procedures were concluded as planned. Mean operative time was 135 min. One patient underwent staged bilateral upper-pole nephrectomy. There were no complications and the postoperative hospital stay was 48 hours in 5 procedures and 24 hours in 2 procedures. Pain medication was required only in the first day. Renal tubular function showed improvement in half of the cases.
Conclusion: Laparoscopic partial nephrectomy is a safe and feasible procedure in infants. Due to the magnification provided by the lenses, a better vision of the structures is achieved, facilitating selective dissection of vascular upper-pole, renal parenchyma and distal ureter. This approach is less damaging to the lower pole, and is associated to low morbidity and a short hospital stay.

Key words: *laparoscopy; infants; nephrectomy*
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INTRODUCTION

In pediatric practice, the use of minimally invasive surgery is on the rise due to its innumerous advantages over open surgery (1-3). Nephrectomy, which was one of the first laparoscopic procedures performed in children, has gained significant acceptance, especially due to the minimal morbidity, shorter hospital stay and improved cosmesis (1,2,4,5). Since the first report by Jordan and Winslow in 1993, the laparoscopic approach has become the procedure of choice for heminephrectomy (6,7). The retroperitoneal approach was proposed by GILL et al. in 1994 (8), but its use was restricted in infants due to the high incidence of peritoneal perforation (9). The purpose of this study is to report the results of a consecutive series of laparoscopic upper-pole nephroureterectomy proce-

dures, with special emphasis in the function of the remaining kidney.

MATERIALS AND METHODS

Seven upper-pole nephroureterectomies were performed in six infants between January 2002 and January 2005. Clinical data were obtained by chart review. Age at operation ranged from 5 to 20 months (median: 9.5 months). In the case of a boy with bilateral duplex system, a second procedure was done 5 months after the first surgery. All infants (except one with recurrent urinary tract infection) had a prenatal diagnosis of pyeloureteral duplex system. This diagnosis was confirmed by ultrasonography, voiding cystourethrogram and scintigraphy after birth. The ^{99m}Tc-DMSA scintigraphy revealed duplicity of the renal unit with upper pole exclusion in all cases. Cystogram showed ureterocele in 1 case and one child had vesicoureteral reflux in both units.

The procedure was done as described by Desgrandchamps et al. 1999 (10). The transperitoneal approach was achieved with the patient in the lateral decubitus position with the operative side up and the lumbar region slightly flexed (Figure-1). The peritoneum was insufflated with CO_2 (pressure 12 mmHg). Three trocars were introduced (two 5 mm and one 10 mm). A fourth trocar (2 mm) was used in case a liver retraction was needed (3 cases). After incising along the Toldt's line, the colon was retracted medially and the Gerota fascia was opened. Careful dissection of the ureter of the upper pole avoiding mobilization of ureter of the lower unit was done followed by the transposition of the duplicate ureter over the renal vascular pedicle. The vascular supply of the upper-pole was dissected and ligated with clips and the dysplastic parenchyma was transected with electrocautery, avoiding damage to the lower half of the kidney and to its vascular pedicle. No attempt was made to suture the renal capsule over the open parenchymal surface. Finally, distal ureter was either clipped close to the bladder if reflux was present, or emptied and left opened whenever an ureterocele was present. The retroperitoneal space was sutured and the incisions were infiltrated with bupivacain. The operative time, need for analgesics, time to resume oral feeding and length of hospital stay were assessed. Scintigraphic study to access the tubular function was done usually six months after the surgery.

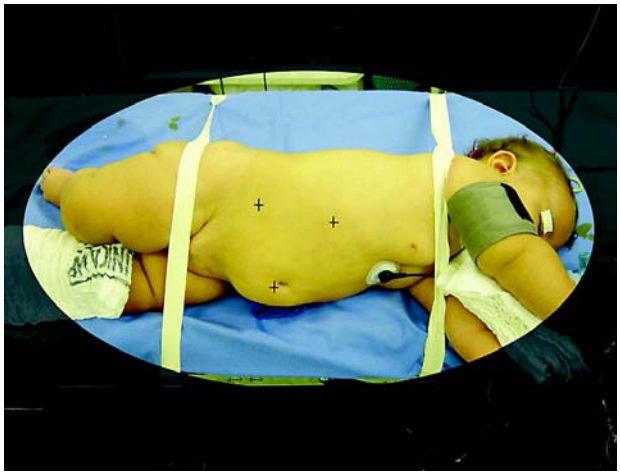

Figure 1 – *Photographic representation of a patient in lateral decubitus showing the location of the trocars.*

RESULTS

All the procedures were completed laparoscopically with a mean operative time of 135 minutes (range: 120 to 160 minutes). The estimated blood loss was minimal and no major per-operative complications were observed. Five infants were fed 4 hours after returning to their beds and the remaining in the day following the surgery. The length of hospital stay was 48 hours for 5 infants and 24 hours for the other 2. Pain medication was required only in the first postoperative day. The histopathological results indicated the presence of renal dysplasia in 3 specimens and chronic pyelonephritis in 4.

Mean follow-up was 18 months. ^{99m}Tc-DMSA scintigraphy showed an improvement or maintenance of tubular function in all infants (Figure-2).

COMMENTS

Because the clinical diagnosis of duplex kidney is presumptive and renal dysplasia of the upper

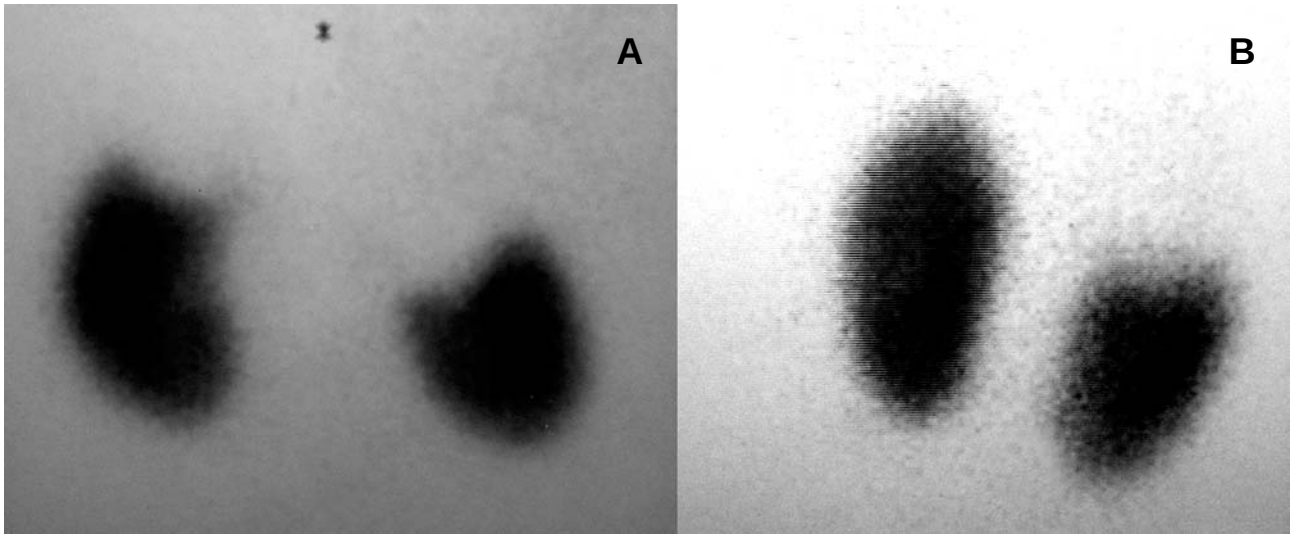

Figure 2 – *Selected IMAGES of the ^{99m}Tc-DMSA showing bilateral upper-pole exclusion on the preoperative (A) and parenchymal accommodation on the postoperative period (B).*

pole may remain asymptomatic, prenatal or incidental sonographic findings have contributed to early diagnosis (11). In this series, 6 out of 7 infants had suspected prenatal diagnosis of duplex system and were therefore referred early to the specialist.

Several surgical approaches to nephrectomy of the upper pole have been described. The classic dorsal lumbotomy approach ensures a great exposure but requires a large incision, intense renal mobilization and is associated to the possibility of atrophy of the remaining kidney (1,5,12). Jednak et al. (2000) described a rapid, safe and easy technique of open heminephrectomy through supracostal approach, which however had to incise parietal muscles and diaphragm to gain greater exposure (13). With the advances and development of appropriated instruments for children, improvement of the techniques with resulting lower rates of morbidity, minimally invasive surgery is becoming common in the pediatric surgery (1,3). An important contribution of video surgery in partial nephrectomy is that the perfect view of the pedicle of both units and delimitation after vascular clamping allows orderly sectioning of the parenchyma, avoiding damage to the intact remaining unit (5,12). Some authors recommend the use of a harmonic scalpel or argon beam coagulator to resect the parenchyma; however, when the vascular delimitation is clear, this section does not represent a problem (1,12). There is still some controversy regarding the choice of either the transperitoneal or retroperitoneal approach. Supporters of the retroperitoneal approach believe that it provides exposure of the posterior aspect of the kidney units, avoiding dissection of the kidney pedicle, which can be preserved (5,14). This approach may be posterior or lateral. Borzi et al. have compared these two approaches and concluded that the posterior approach is preferable for nephrectomies that do not need ureterectomy (9). The lateral approach, on the other hand, provides better access for complete resection of the ureter.

The main inconvenience of the retroperitoneal access is the higher incidence of peritoneal tears in infants, which prevent the creation of an adequate retropneumoperitoneum. This is the most common complication and also the main cause of conversion to open surgery (9,12). In some cases, peritoneal microperforations and consequent ventilatory changes may occur. On the contrary, besides avoiding theses complications, the transperitoneal approach also offers an excellent approach to the vascular bundle with minimum lower pole mobilization and minimal morbidity when compared to retroperitoneal approach (2). Nevertheless, there is no conclusive medical evidence

that favors either the retro or transperitoneal approach (3,15). Like others, we also use the retroperitoneal approach for children over two years of age or to perform a total nephrectomy (14).

The subjectivity of evaluating postoperative pain in children, made analysis of the data very difficult. Reduction of postoperative pain is apparent but very hard to prove in many controlled series (2).

Assessment of the postoperative tubular function has not been stressed in the literature, most probably due to the low incidence of the lesions in the remaining unit. Scintigraphic evaluation is more qualitative than quantitative. In this series, half of the cases presenting with preoperative ureterohydronephrosis and compression of the lower pole, showed recover on postoperative scintigraphy. This observation is probably due to parenchymal accommodation and not to an actual improvement of tubular function. The ^{99m}Tc-DMSA analysis of the tubular function was considered adequate for postoperative evaluation since it demonstrated improved uptake of some renal units, justifying the use of video assisted renal surgery in our service.

Most authors did not observe any difference regarding the surgical duration of laparoscopic heminephrectomy and conventional surgery (5,16). The increase in operative time reported by some is probably related to the learning curve (3,12,16).

CONCLUSION

Minimally invasive approach should be considered when partial nephroureterectomy is indicated, whether through a transperitoneal or a retroperitoneal approach. Magnification makes selective upper-pole dissection safe and feasible, promotes sectioning of the distal ureter without additional incisions, minimizes surgical trauma in the lower pole with minimal morbidity, improving cosmetic results and reducing hospital stay.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Marcio Lopes Miranda
R. Timburí 945
Campinas, SP, 13098-301, Brazil
E-mail: marciomiranda@terra.com.br

EDITORIAL COMMENT

The authors performed upper pole nephrectomy by laparoscopy in children under two years old and achieved good results. The authors are to be congratulated for their efforts in light of the fact that few articles have been published on this subject. However, I would like to comment on some of the thoughts and conclusions made by the authors. First, despite its common usage, the term "minimally invasive procedure" is not an accurate manner to address the laparoscopic upper pole nephrectomy because except for skin incision all the following steps are the same as the open surgery. Because the laparoscopic surgery was performed intraperitonially, one could actually consider it as more invasive, since the peritoneum is not entered in the open procedure. Also, a 10 mm trocar is not a small instrument for such a small child. I believe laparoscopic upper pole nephrectomy is the procedure of choice in older children and has been performed on our group at this age. Moreover, I do not agree with the authors' statement that in small children a large incision is needed for open surgery. The benefits of improved cosmesis and rapid recovery remain controversial in younger children and infants, where smaller incisions and quicker recovery tend to be the role in most open procedures (1). In our department we perform in very young children, the technique described by Jednak et al. and do not isolate the vascular pedicle, which minimizes the risk of vascular damage, and lower pole ischemia (2,3). This procedure is fast, the patients are discharged in 24 hours and there is no need for excessive pain medication at this age.

The authors commented that 5 children were discharged within 48 hours and that pain medication was only necessary for 24 hours in all patients. This raises the question, what were these 5 infants doing at the hospital for 24 hours longer if there was no more pain?

The authors reported that there was improvement in renal function on the operated side. However, this is not possible since according to the authors, there was no upper pole function before the operation and all upper pole tissue was removed. There was no comment about the extent of this improvement, but certainly this cannot be attributed to

a better technique. A maximum of 5% difference among two renal DMSA scans would be expected and this is just an artifact and therefore I do not think that renal accommodation is a good explanation.

Furthermore because there is no control group, the authors cannot justify any advantage of upper pole laparoscopy over open surgery. Prospective studies comparing different surgical approaches are warranted.

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Dr. Ubirajara Barroso Jr.
Section of Urology
Federal University of Bahia
Salvador, Bahia
E-mail: ubarroso@uol.com.br

EDITORIAL COMMENT

Partial nephrectomy is an uncommon procedure in children. This study, therefore, is a welcome opportunity to re-visit this problem. Indeed antenatal diagnosis has uncovered many urologic anomalies, including ureteral duplications, which are asymptomatic (6 cases in this series). Nevertheless, spontaneous resolution seems unlikely for most ectopic ureters and ureteroceles (1). So as in this series, in case of duplex system with minimal or non-functioning upper pole, heminephrectomy is recommended for the affected upper pole (2). A subtotal ureterectomy is usually sufficient, certainly when there is no associated ureterocele. Once that established rest the type of approach.

The gold standard approach still uses a classical flank incision. One of the main problems of this type of operation is that it requires a complete mobilization of the kidney and the vessels. However, vessels of babies are prone to spasm. Failure of excretion of the lower pole therefore is the main postoperative complication. Minimal invasive surgery will probably decrease this complication due to better vision of the vessels (magnification) and the fact that heminephrectomy will be done “in situ”. The minimal invasive approach however may be transperitoneal or retroperitoneal (3). The transperitoneal approach, as described in authors’ paper, provides a wider exposition but requires colon mobilization and unnecessary opening of the peritoneum. Complications are described (4). Patient’s position may be lateral as in this series or more frequently supine with a tilted table. The retroperitoneal access is more “natural”, faster in experienced hands, but requires creation of a working space. This way undoubtedly gives the best hilum’s exposition. Conversion rate is higher, in part due to the learning curve and a thin peritoneum in babies (3 and authors).

Postoperative assessment of tubular function is a finding of importance in this paper. The authors

should be encouraged to report longer term-follow up and perhaps to design a study in collaboration with their scintigraphists and nephrologists in order to better understand this phenomenon.

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Dr. Henri Steyaert
Pediatric Surgery and Urology
Lenval Foundation for Children
Nice, France
E-mail: henri.steyaert@lenval.com

Investigative Urology
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Total Laparoscopic Gastrocystoplasty: Experimental Technique in a Porcine Model

Frederico R. Romero, Claudemir Trapp, Michael Muntener, Fabio A. Brito, Louis R. Kavoussi, Thomas W. Jarrett

The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions (FRR, CT, MM, FAB), Maryland, Baltimore, The Department of Urology, North Shore-LIJ Health System (LRK), Long Island, New York and Department of Urology, The George Washington University Medical Center (TWJ), Washington, DC, USA

ABSTRACT

Objective: Describe a unique simplified experimental technique for total laparoscopic gastrocystoplasty in a porcine model.
Material and methods: We performed laparoscopic gastrocystoplasty on 10 animals. The gastroepiploic arch was identified and carefully mobilized from its origin at the pylorus to the beginning of the previously demarcated gastric wedge. The gastric segment was resected with sharp dissection. Both gastric suturing and gastrovesical anastomosis were performed with absorbable running sutures. The complete procedure and stages of gastric dissection, gastric closure, and gastrovesical anastomosis were separately timed for each laparoscopic gastrocystoplasty. The end-result of the gastric suturing and the bladder augmentation were evaluated by fluoroscopy or endoscopy.
Results: Mean total operative time was 5.2 (range 3.5 - 8) hours: 84.5 (range 62 - 110) minutes for the gastric dissection, 56 (range 28 - 80) minutes for the gastric suturing, and 170.6 (range 70 to 200) minutes for the gastrovesical anastomosis. A cystogram showed a small leakage from the vesical anastomosis in the first two cases. No extravasation from gastric closure was observed in the postoperative gastrogram.
Conclusions: Total laparoscopic gastrocystoplasty is a feasible but complex procedure that currently has limited clinical application. With the increasing use of laparoscopy in reconstructive surgery of the lower urinary tract, gastrocystoplasty may become an attractive option because of its potential advantages over techniques using small and large bowel segments.

Key words*: laparoscopy; bladder; gastroplasty; experimental; pigs*
Int Braz J Urol. 2007; 33: 94-9

INTRODUCTION

Introduced by Sinaiko as an experimental study in 1956, (1) gastrocystoplasty was later adapted for clinical practice by Leong and Ong (2,3).

Gastrocystoplasty was initially conceived to avoid complications frequently present when using the small or large bowel segments to augment the bladder, such as excessive mucus production, hyperchloremic metabolic acidosis, and consequent bone rarefaction and growth problems in the pediatric population (1-3).

The emergence of complications caused by gastric secretion, including hematuria-dysuria

syndrome and hypochloremic metabolic alkalosis, as well as necessity for a large abdominal incision to harvest the gastric wedge and anastomose it to the bladder, have restricted the use of gastrocystoplasty (4-6).

Recently, many laparoscopic studies have been performed, in an attempt to minimize the distress of urinary reconstruction, avoiding large incisions and their destructive psychological and physical consequences (7-11). These reports showed the feasibility of bladder augmentation through laparoscopic approach, improving cosmesis and decreasing postoperative morbidity. The majority of these publications have been done using intestinal segments, (8-10) usually with a hand-assisted method (10,11).

To further increase the therapeutic options and to reduce the morbidity of lower urinary tract reconstructive surgery, we describe a unique simplified experimental technique for total laparoscopic gastrocystoplasty in a porcine model.

MATERIAL AND METHODS

Ten female Sus-scrofus domesticus piglets, with an average weight of 65 lb were used in this study. The experiment protocol was approved by the Institutional Animal Care and Use Committee. The animals received nothing per mouth for 12 hours before the procedure. Each animal was premedicated with an intramuscular injection of telazol, ketamine, and xylazine (TKX, 1 mL/50 lb). Once the animals were tranquilized, anesthesia was induced with intravenous thiopental (10 mg/lb) and maintained with isofluorane inhalation (1.5% - 2%).

The animals were positioned supine. Pneumoperitoneum (15 mm Hg) was achieved with a Veress needle at the level of the umbilicus, followed by introduction of three 10 mm trocars under direct vision: in the midline, four fingerbreadths to the right, and four fingerbreadths to the left, at the level of the umbilicus. When necessary, a fourth 5 mm trocar was introduced laterally and in line with the other trocars to assist with suction or traction (Figure-1).

The gastroepiploic arch was identified along the greater gastric curvature. The branches of the right gastroepiploic artery to the anterior and posterior wall of the antrum were carefully mobilized, and transected between hemoclips. The use of electrocautery and unnecessary grasping of the vessels was strictly avoided during this dissection, to prevent injury to the pedicle. Dissection was carried from the origin of the right gastroepiploic artery, at the level of the pylorus, to the beginning of the segment of stomach which was gonna be used as a graft. Adequate mobilization is important to allow enough length for the pedicle to reach the bladder without tension.

After the pedicle was adequately freed, a paper ruler was introduced into the abdomen and a segment of 4 to 6 cm of stomach was identified. The left gastroepiploic artery was transected immediately

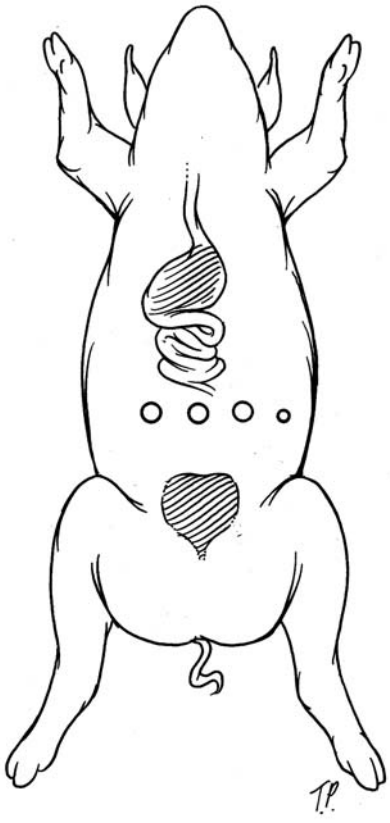

***Figure 1** – Animal positioning and trocar placement in relation to the stomach and the bladder.*

after the distal end of the segment with the use of a linear endoscopic stapler or titanium clips. The wedge-shaped segment of stomach was delineated with electrocautery to facilitate the excision of the graft, beginning at the posterior wall, around the pedicle, and at the anterior wall of the stomach. The apex of the wedge was placed 2 cm away from the lesser gastric curvature to avoid injury to branches of the vagus nerve that control the gastric outlet. Initially, the resection of the gastric wedge was performed by simultaneously cutting the seromuscular and the mucosal layer of the stomach, duplicating the open technique. However, the seromuscular layer retracted behind the mucosa, resulting in redundant mucosal tissue that created difficulties with the visualization of the gastric patch borders during the anastomosis to the bladder. This was solved subsequently by incising the gastric wall in stages. The seromuscular layer was opened first and was easily detached from the underlying mucosa. The mucosal layer was then incised near to the border of the seromuscular patch with the curve of the laparoscopic scissors pointing toward the graft and using slight angulation of the scissors in the same direction, to reduce the amount of mucosal tissue resected.

The native stomach was closed with one layer of running sutures, taking care to invert the gastric mucosa. A stay suture was positioned in the anterior angle of the gastrotomy and pulled outside the abdomen with the assistance of a Carter-Thomason device (Inlet Medical, Eden Prairie, Minnesota, USA), to help in the repair of the stomach and facilitate the placement of the sutures.

The gastric segment was positioned close to the bladder. Care was taken to avoid twisting of the pedicle (Figure-2). The bladder was opened in a sagittal plane in the midline from the bladder neck anteriorly, through the dome, to the trigone posteriorly. Two stay sutures were placed in each side of the bladder to assist in the anastomosis. The first suture was placed in the left lateral aspect of the bladder wall and the right corner of the gastric wedge. With another suture, the right border of the bladder incision was sutured to the left corner of the gastric wedge, and the wedge was approximated to the native bladder. The posterior wall of the anastomosis was performed with absorbable running sutures, with caution to include all the layers of the stomach. After the posterior wall was concluded, the anterior wall of the anastomosis was performed in the same way as with the posterior anastomosis.

At the end of the procedure, a gastrogram was performed with 300 cc of contrast 50%, to confirm closure of the stomach. A cystogram (300 cc of contrast 50%) or cystoscopy under intraabdominal visualization was performed to confirm a watertight bladder reconstruction.

The complete procedure and the stages of gastric dissection, gastric closure, and gastrovesical anastomosis were separately timed for each laparoscopic gastrocystoplasty. The end-result of the

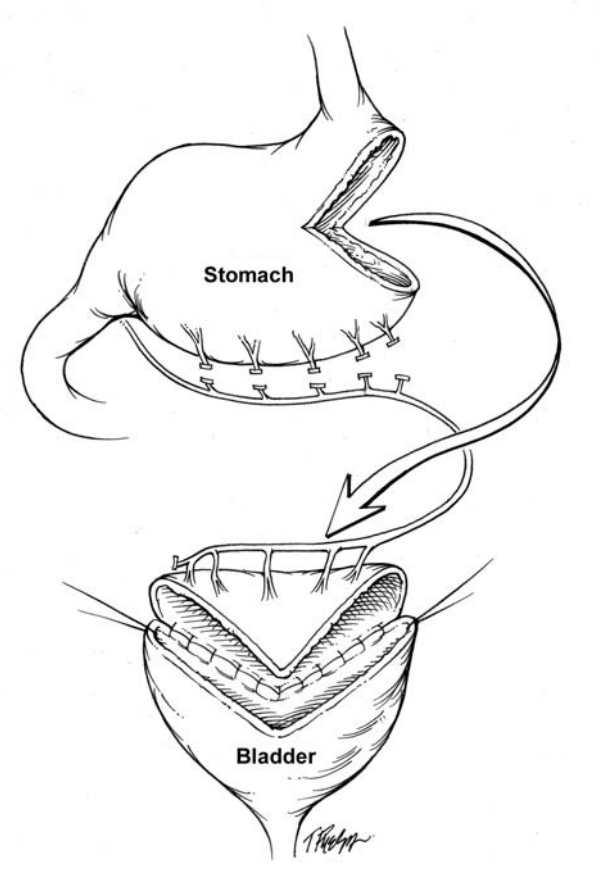

Figure 2 – *The wedge-shaped gastric flap is brought with its blood supply close to the bladder, taking care to avoid twisting of the pedicle (note that all clips are facing the left side of the gastric pedicle).*

gastric suturing and the bladder augmentation were evaluated by fluoroscopy or endoscopy, after which the animals were sacrificed. Postmortem laparotomy was performed to inspect the final result of the gastrocystoplasty.

RESULTS

The mean total operative time was 5.2 hours (range 3.5 to 8 hours). The gastric dissection took an average of 84.5 minutes (range 62 to 110 minutes), the gastric suturing 56 minutes (range 28 to 80 minutes), and the gastrovesical anastomosis 170.6 minutes (range 70 to 220 minutes). Cystogram showed a small leakage from the gastrovesical anastomosis in the first two cases. No extravasation from the gastric closure was observed in the postoperative gastrogram. Laparotomy confirmed these results, showing a defect in the posterior anastomosis as the cause of the bladder leakage in the first two experiments.

COMMENTS

Docimo et al. reported the first laparoscopic bladder augmentation in 1995 (7). Since then, the laparoscopic approach has been increasingly used to perform either augmentation or total replacement of the bladder (8-11). The objectives have been to reduce the morbidity of these complex procedures and to expand laparoscopic reconstructive surgery in both pediatric and adult urology (8-13). Most techniques employ the small or large bowel and maintain the same principles of conventional open surgery. Usually, the intestinal segment is detubularized, refashioned, and sutured to the bladder using either intracorporeal or, most frequently, extracorporeal suturing.

In the past decade, many authors restricted the indications of open gastrocystoplasty because of the increasing appearance of hematuria-dysuria (6,14), despite the small number of patients presenting this complication in several series and the good response to clinical management with proton pump inhibitors (14,15). Another complication reported, the hypocloremic metabolic alkalosis (5), is a rarely seen entity that can be prevented by proper electrolyte correction in the management of acute diarrhea. Despite these particular complications, the stomach is a useful alternative in selected patients with a poorly compliant or a high-pressure bladder that need bladder augmentation. Short bowel syndrome, renal insufficiency with metabolic acidosis, and previous pelvic irradiation are clinical situations in which gastrocystoplasty would be the preferred form of bladder augmentation (2,4,15,16). Other situations in which gastrocystoplasty may be used include the necessity for a pouch with less mucous production and in patients with recurrent urinary lithiasis (3,17).

With the increasing use of laparoscopy in reconstructive surgery of the lower urinary tract, gastrocystoplasty may be an attractive option because of its advantages over the techniques using small and large bowel segments. It eliminates the need of detubularization and refashioning of the bowel, reducing the amount of intracorporeal suturing. Also, in contrast to other intestinal segments, the gastric flap is more similar to the bladder wall in thickness, facilitating an even coaptation during the anastomosis.

Pure laparoscopic gastrocystoplasty is a feasible procedure (7). The porcine experimental model duplicates the anatomy of the gastric and urinary tracts in humans relatively well, and it is known to be a good training modality for advanced laparoscopic techniques. Although this was not a survival study, this simplified surgical technique may enable surgeons to practice both dissection and suturing skills required in extirpative and reconstructive laparoscopic surgery. If this were a survival procedure, some important technical aspects should be pointed. Although intracorporeal gastric suturing is a well-established technique for gastric closure and it is specially useful for surgical skills training, laparoscopic stapling of the stomach avoids the risk of peritoneal contamination and allows for a faster gastric wedge resection. The gastric patch pedicle should be retroperitonealized by releasing the right colon medialy and lying the right gastroepiploic pedicle in the retroperitoneum. The augmented bladder should be drained by suprapubic cystostomy,

and two abdominal drains should also be placed through the ports to drain gastric and bladder sutures.

Regardless of the gastrointestinal segment chosen, several benefits are obtained with the laparoscopic approach. Decreased perioperative morbidity, less need for postoperative analgesics, faster recovery time, and improved cosmetic results are the main advantages favoring laparoscopy over the open techniques (7,8,13). Furthermore, advancements in tissue engineering technology may allow the use of demucosalized gastric segments as a vehicle to transport in vitro expanded urothelial cells during bladder reconstruction (18,19). The ease with which the gastric mucosa can be detached from the seromuscular layer of the stomach may allow gastrocystoplasty to be a handy transport matrix.

The development of the laparoscopic approach and the recent advancements in tissue engineering may allow demucosalized gastrocystoplasty to be applied more extensively in the near future, avoiding the complications inherent to the gastric mucosa.

CONCLUSIONS

Total laparoscopic gastrocystoplasty is a feasible but complex procedure that currently has limited clinical application. With the increasing use of laparoscopy in reconstructive surgery of the lower urinary tract, gastrocystoplasty may become an attractive option because of its potential advantages over the techniques using bowel segments. Additional survival and clinical studies, specially with the use of the modified demucosalized technique with urothelial cells grafting, are necessary to evaluate the perspectives of laparoscopic gastrocystoplasty in the future.

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CONFLICT OF INTERERST

None declared.

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Correspondence address:
Dr. Frederico Ramalho Romero
The Johns Hopkins Medical Institutions
The James Buchanan Brady Urological Institute
600 North Wolfe Street, Marburg 1
Baltimore, Maryland, 21287, USA
Fax: + 1 410 502-7711
E-mail: frederico.romero@gmail.com

EDITORIAL COMMENT

Augmentation cystoplasty is needed to treat some congenital pediatric and adult urological diseases. Although several substitutes have been employed, the vascularized intestinal segments are still the most commonly used tissue for this reconstruction, despite the described long-term complications. The minimally invasive approach for bladder augmentation has been described and may decrease the perioperative morbidity of this procedure (1).

The authors described a minimally invasive technique for gastrocystoplasty in a non-survival porcine model and should be congratulate for their initiative. Despite the authors' large experience in advanced laparoscopic cases, the mean operative time extended 5 h, most due to the gastrovesical anastomosis (3 h), with posterior wall leakage occurring in the initial 2 cases of this series. One alternative to this problem would be a laparoscopic-assisted technique, employing the laparoscopic access to dissect and isolate an adequate gastric segment, performing the anastomosis through a small abdominal incision, in the same fashion as the reconstructive part of current technique of laparoscopic radical cystectomy (2).

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Dr. Jose R. Colombo Jr.
Section of Laparoscopic and Robotic Surgery
Glickman Urological Institute, Cleveland Clinic
Cleveland, Ohio, USA
E-mail: columbj@ccf.org

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Re: Laparoscopic-Assisted Nephroureterectomy after Radical Cystectomy for Transitional Cell Carcinoma

Frederico R. Romero, Michael Muntener, Sompol Permpongkosol, Louis R. Kavoussi, Thomas W. Jarrett

The James Buchanan Brady Urological Institute (FRR, MM), Baltimore, Maryland, Department of Urology, North Shore-LIJ Health System (LRK), Long Island, New York and Department of Urology, The George Washington University Medical Center (TWJ), Washington, DC, USA

Int Braz J Urol, 32: 631-9, 2006

To the Editor:

To the best of my knowledge, this is the first extensive report on the outcome of laparoscopic nephroureterectomy in patients with a prior radical cystectomy. While the authors were successful in performing the procedure with laparoscopic assistance in 6 of 7 patients, the procedures were lengthy, associated with intraoperative complications in 28% of patients, postoperative complications in 28% of patients, and the need for an open incision through the prior cystectomy site in all cases in order to remove the distal cuff of bladder. It is of note that 3 of the 4 complications that occurred were associated with the opening of the old incision in all patients to deal with the distal ureter. The overall difficulty of the dissection is reflected in the 10.8 days of hospital stay. Unfortunately, there was no comparison made to an open cohort treated in a similar manner.

This report is reminiscent of the initial articles on laparoscopic surgery for xanthogranulomatous pyelonephritis. In those early studies, no benefit to the laparoscopic approach could be found; however, with time and experience, the results have improved to the point where the laparoscopic approach is today the justifiably preferred method at most laparoscopic centers. I would anticipate a similar scenario would evolve for this difficult type of nephroureterectomy.

What will make the difference? I would opine that other laparoscopic surgeons might elect to begin the procedure with a retroperitoneoscopic approach to the kidney as has been championed by several investigators such as Drs. Ono, Gill, and others. This would preclude dealing with many of the intra-abdominal adhesions and could possibly result in a shorter period of ileus. Secondly, it might be helpful to place a large external ureteral catheter via the conduit prior to embarking on the procedure. This could help with identification and dissection of the ureter especially at the level of the diversion.

In sum, I congratulate the authors on providing an honest sobering report of their initial experience with postcystectomy nephroureterectomy. It is obvious that this approach is in its earliest stages. While the authors have shown that this procedure is feasible, it, at this point in time, does not appear to be better than the standard open approach.

Dr. Ralph V. Clayman
Professor and Chair, Department of Urology
University of California, Irvine Medical Center
Orange, California, USA
E-mail: rclayman@uci.edu

International Braz J Urol Vol. 33 (1):101-124, January - February, 2007

UROLOGICAL SURVEY

Francisco J.B. Sampaio
Urogenital Research Unit
State University of Rio de Janeiro

Athanase Billis
State University of Campinas
Campinas, SP, Brazil

Andreas Böhle
Helios Agnes Karll Hospital
Bad Schwartau, Germany

Steven B. Brandes
Washington University in St. Louis
St. Louis, Missouri, USA

Fernando J. Kim
Univ Colorado Health Sci Ctr
Denver, Colorado, USA

Manoj Monga
University of Minnesota
Edina, MN, USA

Steven P. Petrou
Mayo Medical School
Jacksonville, Florida, USA

Adilson Prando
Vera Cruz Hospital
Campinas, SP, Brazil

Brent W. Snow
University of Utah
Salt Lake City, Utah, USA

Arnulf Stenzl
University of Tuenbingen
Tuebingen, Germany

STONE DISEASE

Miniperc? No, Thank You!

Giusti G, Piccinelli A, Taverna G, Benetti A, Pasini L, Corinti M, Teppa A, Zandegiacomo de Zorzi S, Graziotti P
Department of Urology, Istituto Clinico Humanitas, IRCCS, Milan, Italy
Eur Urol. 2007; 51: 810-5

Objectives: The aim of this retrospective study was to evaluate the results of our miniperc series through comparison with results from standard percutaneous nephrolithotomy (PNL) and tubeless PNL series in the treatment of stones < 2cm in diameter.
Patients and Methods: A total of 134 percutaneous treatments were performed for renal stones < 2cm in diameter. Among the treatments, 40 were minipercs, 67 were standard PNLs, and 27 were tubeless PNLs.
Results: Miniperc operative time was longer than that of standard PNL (155.5 vs 106.6 min, respectively) and tubeless PNL (95.9min). Conversely, there was an advantage for miniperc over standard PNL in terms of a significantly reduced hematocrit drop (4.49% vs 6.31%). No miniperc patients required blood transfusions, whereas two did in the standard PNL group and one in the tubeless PNL group. There was no statistical difference in terms of the amount of analgesics between the standard PNL and miniperc groups, although this difference was statistically significant between the miniperc and tubeless PNL groups (73.8 vs 41.1 mg, respectively). Hospitalization for the miniperc group was shorter than that required by the standard PNL group (3.05 vs 5.07 days), but tubeless PNL offered the best result (2.18 days). The stone-free rate was 100% in the tubeless PNL group, 94% in the standard PNL group, and 77.5% in the miniperc group.
Conclusions: Our retrospective study failed to demonstrate significant advantages of the miniperc technique. As such, we no longer perform miniperc but instead use tubeless PNL when possible.

Editorial Comment

As an early proponent of a mini-PCNL, the main advantage I anticipated with a mini-PCNL was a decrease in blood loss. Indeed, this hypothesis is supported by the current study. As it stands, decrease in blood loss would be an outcome worth striving for, yet not at the expense of lower stone-free rates. Improvements in instrumentation, in particular smaller ultrasonic devices, are needed to help raise the success rate of mini-PCNL to the expected standard. The issue of pain post-PCNL will be decided more by the size of tube than the size of tract - many studies now support the use of a small-bore or tubeless approach to minimize this aspect of PCNL-associated morbidity. As such, one might rephrase the title from “No, Thank You” to “Not Yet”. If the future brings improvement in instrumentation, one might anticipate that a tubeless mini-PCNL may resurface.

Dr. Manoj Monga
Professor, Department of Urology
University of Minnesota
Edina, Minnesota, USA

Acute Effects of Percutaneous Tract Dilation on Renal Function and Structure

Handa RK, Matlaga BR, Connors BA, Ying J, Paterson RF, Kuo RL, Kim SC, Lingeman JE, Evan AP, Willis LR
Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, Indiana, USA
J Endourol. 2006; 20: 1030-40

Background: Percutaneous nephrolithotomy (PCNL) is performed on a routine basis for the rapid and efficient removal of large caliceal stones. After percutaneous puncture, rigid dilators or an inflatable balloon are used to dilate the nephrostomy tract to allow access to the collecting system for stone removal. Little is known of the acute impact of tract dilation procedures on renal function.
Materials and Methods: We compared renal hemodynamic and excretory function in female pigs immediately before and up to 5 hours after percutaneous nephrostomy (PCN) using sequential Amplatz dilators (N = 8) or Nephromax balloon inflation (N = 7) and control pigs with no PCN access (N = 8). We also examined renal function in patients undergoing PCNL.
Results: The two PCN procedures produced a renal lesion of comparable size and morphology, as well as similar changes in renal function. Glomerular filtration rate (GFR), renal plasma flow (RPF), and urinary sodium excretion (U(Na)V) were significantly reduced in Amplatz- and Nephromax-treated kidneys throughout the 5-hour observation period, by about 50%, 60%, and 80%, respectively. In control pigs, GFR and RPF remained stable and U(Na)V declined progressively to about 50% of baseline over the course of the experiment. The contralateral kidney showed changes in renal function similar to those in the PCN-treated or control kidney in all three groups. A retrospective analysis of 196 adults with normal renal function who underwent unilateral PCNL using the Nephromax balloon dilator revealed a significant increase in serum creatinine of 0.14 mg/dL at 1 day.
Conclusion: Both animal and human studies show that PCN is associated with an acute decline in renal function.

Editorial Comment
This study raises concern regarding transient decrease in ipsilateral and contralateral renal function during PCNL. The authors did not have a control group where percutaneous access was gained with a puncture needle, but the tract was not dilated. Such a group would help delineate whether the insult to the kidney leading to hemodynamic and functional changes is the percutaneous access or tract dilation. Renal obstruction may have confounded the results obtained during the evaluation period - it is possible that the 8F Cope catheter and ureter may have been blocked by clots associated with the tract dilation. Indeed the authors report a marked decrease in urine output in these animals, with 2 animals experiencing complete cessation of urine formation from the treated kidney. Future studies evaluating the relative changes in function with regards to maximum diameter of tract dilation may help support or refute the concept of a mini-PCNL. As such, these findings are critical for the practicing urologist to appreciate, as the impact on ipsilateral and contralateral renal filtration, perfusion and excretory function suggests a need to monitor the use of nephrotoxic medications, such as ketorolac or gentamycin, during the immediate post-PCNL period.

Dr. Manoj Monga
Professor, Department of Urology
University of Minnesota
Edina, Minnesota, USA

ENDOUROLOGY & LAPAROSCOPY

Preoperative and Intraoperative Risk Factors for Side-Specific Positive Surgical Margins in Laparoscopic Radical Prostatectomy for Prostate Cancer

Secin FP, Serio A, Bianco FJ Jr, Karanikolas NT, Kuroiwa K, Vickers A, Touijer K, Guillonneau B
Department of Urology, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
Eur Urol. 2007; 51: 764-71

Objectives: Identification of variables predicting positive surgical margins (PSMs) in patients undergoing laparoscopic radical prostatectomy (LRP) for clinically localized prostate cancer is lacking. Our objective was to determine preoperative risk factors and the association of ipsilateral degree of neurovascular bundle dissection (intraoperative factor) with side-specific PSMs in these patients.
Material and Methods: Between October 2002 and April 2005, one surgeon performed LRP on 407 previously untreated patients. Of 814 evaluable prostate sides, 728 harboured prostate cancer in the specimen and composed the study population. For each prostate side, we obtained clinical stage, biopsy Gleason, maximum percentage of tumour in the biopsy, suspected extracapsular extension (ECE) on endorectal coil magnetic resonance imaging (MRI), degree of neurovascular bundle (NVB) dissection, and PSMs. PSM was defined as cancer cells at the inked margins. Logistic regression analyses with random effects were generated.
Results: Of the 728 prostate sides with cancer, 51 (7%) had at least one PSM. In multivariable analysis, higher PSA (p=0.01), Gleason score of 7 compared with </=6 in the biopsy (p=0.04), lower prostate volume on MRI (p=0.01), and interfascial NVB dissection compared with intrafascial dissection (p=0.01) were associated with an increased risk of side-specific PSMs. Suspected ECE on MRI (p=0.9) and clinical stage (p=0.3) were not significantly associated with side-specific PSMs. A subset analysis of 321 patients with bilateral tumours did not show statistically significant differences in PSMs according to tumour side (p=0.3).
Conclusions: High serum prostate-specific antigen, biopsy Gleason score of 7, low prostate volume, and interfascial NVB dissection were independently associated with side-specific PSMs after LRP, and should be considered during planning of the LRP surgical strategy.

Editorial Comment
Preoperative PSA, clinical stage, and biopsy Gleason score can predict positive surgical margins preoperatively. Furthermore, a positive surgical margin has been shown to be associated with biochemical recurrence rates up to 50% at 10 years after radical prostatectomy. The authors present their experience in improving the surgical technique to optimize clinical outcome and survival. Their conclusion states that neurovascular bundle preservation is not a risk factor for increase rates of positive margins when the technique is applied adequately in selected patients. Other factors such as elevated serum PSA (> 10 ng/mL), small glands (< 30 g), biopsy Gleason scores of 7, degree of neurovascular bundle dissection, and presence of bulky disease should be considered by laparoscopic surgeons when planning the operation to decrease the incidence of positive surgical margins.

Dr. Fernando J. Kim
Chief of Urology, Denver Health Med Ctr
Assistant Professor, Univ Colorado Health Sci Ctr
Denver, Colorado, USA

Limitations of Laparoscopy for Bilateral Nephrectomy for Autosomal Dominant Polycystic Kidney Disease

Lipke MC, Bargman V, Milgrom M, Sundaram CP
Department of Urology, Indiana University School of Medicine, Indianapolis, Indiana 46202-5289, USA
J Urol. 2007; 177: 627-31

Purpose: We retrospectively studied outcomes following bilateral hand assisted laparoscopic nephrectomy.
Materials and Methods: We retrospectively reviewed the charts of 18 patients with symptomatic autosomal dominant polycystic kidney disease who underwent bilateral hand assisted laparoscopic nephrectomy.

Preoperative radiographic imaging was reviewed retrospectively to determine kidney size based on an ellipsoid shape. A visual analog pain scale with scores of 0 to 10 to assess pain related to autosomal dominant polycystic kidney disease was measured preoperatively and postoperatively.
Results: Average patient age was 48.2 years (range 30 to 64). Of the patients 14 successfully underwent bilateral hand assisted laparoscopic nephrectomy, while 4 required open conversion. A total of 16 patients underwent nephrectomy for pain and 2 underwent surgery for frequent recurrent symptomatic urinary tract infections. All patients except 1 underwent renal transplantation before bilateral nephrectomy. There was a significant difference in the volume of the right and left kidneys between the hand assisted laparoscopic and open groups (mean +/- SD 1,043 +/- 672 and 1,058 +/- 603.8 vs 4,052 +/- 548 and 3,592 +/- 1,752 cm (3), $p < 0.001$ and 0.06 respectively). There were 5 complications, including wound infection and protracted ileus in 2 patients each, and incisional hernia in 1. In addition, the difference in mean preoperative and postoperative visual analog pain scores was statistically significant (6.9, range 3 to 10 and 0.5, range 0 to 2, $p < 0.05$).
Conclusions: Bilateral laparoscopic hand assisted nephrectomy is a safe and reliable option in patients requiring removal of the 2 kidneys in a single setting. Rather than performing staged nephrectomies, hand assisted laparoscopic nephrectomy allows the single administration of general anesthesia and provides effective relief of bothersome symptoms in patients with symptomatic autosomal dominant polycystic kidney disease. This procedure is safe in patients with renal transplants. Patients with massive polycystic kidneys with a kidney volume of greater than 3,500 cc are at increased risk for open conversion and they may have improved outcomes if open nephrectomy is attempted from the outset.

Editorial Comment
The new era of minimally invasive surgery demonstrates the feasibility of bilateral nephrectomies performed laparoscopically. There are no more questions that patients recover faster with better outcomes than the open counterpart is. Moreover, this less invasive approach allows patients to undergo 2 procedures in one setting providing innumerous benefits to patients that in the past had to experience staged operations. The authors demonstrated limitations to the technique when the polycystic kidneys are massively large decreasing the working space.

Dr. Fernando J. Kim
Chief of Urology, Denver Health Med Ctr
Assistant Professor, Univ Colorado Health Sci Ctr
Denver, Colorado, USA

IMAGING

Conscious Sedation Reduces Distress in Children Undergoing Voiding Cystourethrography and Does Not Interfere With the Diagnosis of Vesicoureteric Reflux: A Randomized Controlled Study

Herd DW, McAnulty KA, Keene NA, Sommerville DE
Department of Radiology, Waikato Hospital, Hamilton, New Zealand
AJR Am J Roentgenol. 2006; 187: 1621-6

Objective: Voiding cystourethrography (VCU) is a distressing procedure for children. Conscious sedation using oral midazolam may reduce this distress, but its use may also alter the ability of the VCU to show vesicoureteric reflux (VUR). The objectives of our study were to assess the effectiveness of conscious sedation using oral midazolam when administered routinely in children undergoing VCU and to ensure that conscious sedation using oral midazolam does not alter the ability of VCU to show VUR.

Subjects and Methods: Our study was a randomized double-blind controlled trial performed at a university teaching hospital; our study group consisted of children over the age of 1 year who been referred for their first VCU examination from July 2001 to July 2003. Participants were randomized to receive a placebo or midazolam syrup (0.5 mg/kg) before the examination. The primary outcome measures were the Groningen Distress Rating Scale (GDRS) and grading of VUR, as defined by the international grading system established by the International Reflux Study Group.
Results: There were no serious adverse events. One hundred thirty-nine children were randomized in the study, and 117 underwent complete assessment. Eight who underwent VCU after the study day were included in a "complete case" intention-to-treat analysis. In the placebo group, 34 children (61%) experienced serious distress or severe distress (GDRS score, 3 or 4). In the midazolam group, 16 children (26%) experienced the same degree of distress. There was a significant difference between the GDRS scores (nonlinear mixed-model analysis, $p < 0.001$) of the two study groups. The number needed to treat to reduce serious or severe distress in one child was 2.9 (95% CI, 1.9-5.5). VUR was identified in 16% of all children. There was no difference in VUR grading between the groups (nonlinear mixed-model analysis, $p = 0.31$).
Conclusion: Routine use of oral midazolam (0.5 mg/kg) for conscious sedation of children undergoing VCU reduces distress and does not alter the ability of VCU to show VUR well enough to allow diagnosis.

Editorial Comment

In children, the voiding cystourethrogram (VCUG) although a stressful experience for patients and their parents, is an exam relatively easy to perform by an experienced radiologist. Usually no preparation is needed for children; no cleansing enema, fasting or anesthesia is required. In fact, up to now, the vast majority of radiologists prefers to perform this examination when the child is awake. In selected group of children, particularly those who are excessively frightened (previous VCUG), oral midazolam has been used sporadically in order to reduce anxiety and produce antegrade amnesia (1). In 2003, a randomized double blind study (oral midazolam and placebo) performed in 95 children showed that there was no difference in frequency or grade of vesicoureteric reflux or bladder emptying between the two groups of patients(2). We must emphasize that good results has been obtained only with oral midazolan and not with other drugs. Recent study showed that children who underwent VCUG with sedation using propofol were less likely to void to completion thus impairing the ability to accurately detect vesicoureteral reflux (3).

The authors of this important study clearly shows that sedation with midazolam facilitates the performance of VCUG in children above 1 year of age, with no impairment in the capacity of detect vesicoureteric reflux. We believe that sedation with oral midazolam should be routinely used in children candidate for VCUG examination since it reduce the stress and has no negative effect on the outcome of the examination.

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Dr. Adilson Prando
Chief, Department of Radiology
Vera Cruz Hospital
Campinas, São Paulo, Brazil

Surgically Relevant Normal and Variant Renal Parenchymal and Vascular Anatomy In Preoperative 16-MDCT Evaluation of Potential Laparoscopic Renal Donors

Raman SS, Pojchamarnwiputh S, Muangsomboon K, Schulam PG, Gritsch HA, Lu DS
Department of Radiology, David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles, CA, USA
AJR Am J Roentgenol. 2007; 188: 105-14

Objective: Using 16-MDCT, we describe and quantify the frequency and types of renal anatomic variants and findings relevant for preoperative evaluation and surgical planning for potential laparoscopic renal donors.
Materials and Methods: On 16-MDCT, 126 consecutive potential donors underwent scanning before contrast administration and after i.v. power injection of nonionic contrast material during the arterial, nephrographic, and excretory phases. On a 3D workstation, CT images were evaluated retrospectively in consensus by three abdominal imagers. The number and branching pattern of bilateral renal arteries and veins, including anomalies of the inferior vena cava and lumbar-gonadal axis, were categorized along with the frequency of incidental findings of the renal parenchyma and collecting system.
Results: Major arterial variants including supernumerary and early branching arteries were present in 16% and 21%, respectively, of left kidneys and 22% and 15%, respectively, of right kidneys. Major and minor venous variants were detected in 11% and 58% of left kidneys and 24% and 3% of right kidneys. Late confluence of the venous trunk was identified in 17% of left kidneys and 10% of right kidneys. Incidental parenchymal and urothelial abnormalities, most commonly cysts and calyceal calcifications, were identified in 30% of the kidneys. Other relevant incidental findings included focal infarcts, cortical scars, atrophic scarred kidney, and bilateral papillary necrosis. Urothelial variants included bilateral simple ureteroceles and rightsided complete duplicated collecting system.
Conclusion: 16-MDCT angiography and urography allow confident detection and classification of a variety of anatomic and incidental anomalies relevant to the preoperative selection of potential laparoscopic renal donors and to surgical planning.

Editorial Comment

In most transplantation centers, multi–detector row computed tomography (MDCT), is used as the sole imaging technique in the preoperative evaluation of living renal donors. With 16-row-MDCT an increased number of simultaneously acquired slices and sub-millimeter collimation allows a near isotropic scanning with high spatial resolution thus providing exquisite multiplanar reconstructions of the kidneys and the vascular anatomy.

The authors nicely show the value of 16-row-MDCT for the preoperative knowledge of renal vascular, parenchymal and urothelial anatomy and their importance for donor and kidney selection. 16-row-MDCT angiography and urography, enabled excellent preoperative information, which are essential since it helps laparoscopic surgeons to anticipate variant anatomy intraoperatively and avoid potential donor complications.

Dr. Adilson Prando
Chief, Department of Radiology
Vera Cruz Hospital
Campinas, São Paulo, Brazil

UROGENITAL TRAUMA

Predicting Urethral Injury from Pelvic Fracture Patterns in Male Patients with Blunt Trauma

Basta AM, Blackmore CC, Wessells H
Department of Radiology, Harborview Injury Prevention and Research Center, Harborview Medical Center, University of Washington, Seattle, Washington, USA
J Urol. 2007; 177: 571-5

Purpose: Precise definition of pelvic fracture location may enable prediction of which subjects are at risk for urethral injury and understanding of the pathophysiological mechanism of injury. We determined the specific anterior pelvic injury locations associated with urethral injury.
Materials and Methods: We completed a retrospective, nested case-control study of 119 male patients evaluated at a single large level 1 trauma center between January 1, 1997 and July 15, 2003. We performed detailed measurements of the location, displacement and direction of force of each anterior pelvic fracture from computerized tomography and pelvic radiographs. Multiple logistic regression was used to determine associations between specific fracture locations and urethral injury after controlling for age, injury mechanism, injury severity and direction of force.
Results: Urethral injury was present in 25 patients and all had anterior pelvic fracture (inclusive of pubic symphysis diastasis). There were no urethral injuries in patients with fractures isolated to the acetabulum. Pelvic fractures that were independently associated with urethral injury from multiple regression analysis included displaced fractures of the inferomedial pubic bone, OR 6.4 (95% CI 1.6 to 24.9), and symphysis pubis diastasis, OR 11.8 (95% CI 4.0 to 34.5). Each millimeter of symphysis pubis diastasis or inferomedial pubic bone fracture displacement was associated with an approximately 10% increased risk of urethral injury.
Conclusions: The location and displacement of anterior pelvic fractures in males predict risk of urethral injury and may be valuable in determining when evaluation of the urethra is appropriate.

Editorial Comment

This study adds to the body of literature that demonstrates that urethral injury associated with pelvic fracture, typically occurs when the anterior pelvic arch is disrupted that results in symphysis diastasis and displaced pubic rami fractures. The biomechanics of urethral injury as originally described by Turner-Warwick felt that the disruption was prostatomembranous, with the prostate displaced from the fixed urogenital diaphragm. Over time, however, it has been recognized that many injuries are rather to the bulbo-membranous junction, and not at the prostate level. Prior to this study the most commonly sited paper was by Koraitim (ref. 10 in article) where the highest odds ratios for urethral injury were with straddle injury and SI fracture. A paper correlating fracture by the Young-Burgess or Tile classification and urethral injury would have been nice.

Dr. Steven B. Brandes
Associate Professor, Division of Urologic Surgery
Washington University in St. Louis
St. Louis, Missouri, USA

Accuracy of Trauma Ultrasound in Major Pelvic Injury

Tayal VS, Nielsen A, Jones AE, Thomason MH, Kellam J, Norton HJ
Department of Emergency Medicine, Carolinas Medical Center, Charlotte, NC, USA
J Trauma. 2006; 61: 1453-7

Background: Trauma ultrasound (US) utilizing the focused assessment with sonography in trauma (FAST) is often performed to detect traumatic free peritoneal fluid (FPF). Yet its accuracy is unclear in certain trauma subgroups such as those with major pelvic fractures whose emergent diagnostic and therapeutic needs are unique. We hypothesized that in patients with major pelvic injury (MPI) trauma ultrasound would perform with lower accuracy than has previously been reported.
Methods: Retrospective analysis of adult trauma patients with pelvic fractures seen at an urban Level I emergency department and trauma center. Patients were identified from the institutional trauma registry and ultrasound database from 1999 to 2003. All patients aged > 16 years with MPI (Tile classification A2, all type B and C pelvic fractures, and type C acetabular fractures determined by a blinded orthopedic traumatologist) and who had a trauma US performed during the initial emergency department evaluation were included. All ultrasounds were performed by emergency physicians or surgeons using the four-quadrant FAST evaluation. Results of US were compared with one of three reference standards: abdominal/pelvic computed tomography, diagnostic peritoneal tap, or exploratory laparotomy. Two-by-two tables were constructed for diagnostic indices.
Results: In all, 96 patients were eligible; 9 were excluded for indeterminate ultrasound results. Of the remaining 87 patients, the pelvic fracture types were distributed as follows: 9% type A2, 72% type B, 16% type C, and 3% type C acetabular fractures. Overall US sensitivity for detection of FPF was 80.8%, specificity was 86.9%, positive predictive value was 72.4%, and negative predictive value was 91.4%. Categorization of sensitivity according to pelvic ring fracture type is as follows: type A2 fractures: sensitivity and specificity, 75.0%; type B fractures: sensitivity, 73.3%, specificity, 85.1%; and type C fractures (pelvis and acetabulum): sensitivity and specificity, 100%. Of the true-positive US results, blood was the FPF in 16 of 21 (76%) and urine from intraperitoneal bladder rupture in 4 in 21 (19%) patients.
Conclusion: US in the initial evaluation of traumatic peritoneal fluid in major pelvic injury patients has lower sensitivity and specificity than previously reported for blunt trauma patients. Additionally, uroperitoneum comprises a substantial proportion of traumatic free peritoneal fluid in patients with MPI.

Editorial Comment
The true value of FAST is in the evaluation for blood in the pericardial sac, hepatorenal fossa, splenorenal fossa, and the pelvis. One limitation of FAST is its inability to distinguish between a urine leak and blood. Overall, FAST is a quick and easy way to determine the source of bleeding in an unstable patient — from the chest, the abdomen or the pelvis.

Dr. Steven B. Brandes
Associate Professor, Division of Urologic Surgery
Washington University in St. Louis
St. Louis, Missouri, USA

PATHOLOGY

Spindle Cell Lesions of the Adult Prostate

Hansel DE, Herawi M, Montgomery E, Epstein JI
Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD, USA
Mod Pathol. 2007; 20: 148-58

Prostatic spindle cell lesions are diagnostically challenging and encompass a broad array of benign and malignant processes. A subset of these lesions arises only within the prostate and generally represents entities

that originate from the prostate epithelium or stroma, such as sclerosing adenosis, sarcomatoid carcinoma, stromal tumors of uncertain malignant potential (STUMP), and stromal sarcoma. Another subset of spindle cell tumors that involve the prostate are also found at other sites and include solitary fibrous tumor, leiomyosarcoma, and neural lesions among others. Finally, tumors may secondarily involve the prostate yet present as primary prostatic processes, as is evident with several cases of gastrointestinal stromal tumors (GIST). The utility of ancillary studies, including immunohistochemistry, is often limited and the main criteria for diagnosis are the morphologic findings by routine H&E stain. This review addresses the various entities that may present as spindle cell tumors within the adult prostate and discusses the functional aspects of the differential diagnosis of these lesions.

Editorial Comment

Spindle cell lesions are rare in the prostate. Among these lesions is worth commenting for the urologists sarcomatoid carcinoma and the lesions proposed by the authors to be called STUMP. There is a lot of debate in the literature about the terms sarcomatoid carcinoma vs. carcinosarcoma. These terms apply to tumors that show spindling of the cells sometimes with heterologous differentiation like osteosarcoma, condrosarcoma, angiosarcoma and others. There is a tendency to call these cases sarcomatoid carcinoma with heterologous differentiation based on studies that show a monoclonal origin for these tumors.

Stromal tumors of uncertain malignant potential (called by the authors STUMP) encompass a group of lesions that most of the times are hard to establish histologically the biological behavior in contrast to frankly sarcomatous lesions like leiomiosarcoma, rabdomiosarcoma and others. STUMP includes several patterns of lesions originating from the specialized stroma of the prostate: phyllodes tumor of the prostate, hypercellular stroma with scattered atypical yet degenerative cells, and extensive overgrowth of hypercellular stroma with the histology of a stromal nodule (1). STUMPS are considered neoplastic, based on the observations that they may diffusely infiltrate the prostate gland and extent into adjacent tissues, and often recur. Although most cases of STUMP do not behave in an aggressive fashion, occasional cases have been documented to recur rapidly after resection and a minority has progressed to stroma sarcoma.

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Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, Sao Paulo, Brazil

Inflammatory Myofibroblastic Tumors of the Urinary Tract: A Clinicopathologic Study of 46 Cases, Including a Malignant Example Inflammatory Fibrosarcoma and a Subset Associated With High-Grade Urothelial Carcinoma

Montgomery EA, Shuster DD, Burkart AL, Esteban JM, Sgrignoli A, Elwood L, Vaughn DJ, Griffin CA, Epstein JI
Department of Pathology, Johns Hopkins Hospital, Baltimore, USA
Am J Surg Pathol. 2006; 30: 1502-12

Inflammatory myofibroblastic tumor (IMT) of the urinary tract, also termed postoperative spindle cell nodule, inflammatory pseudotumor, and pseudosarcomatous fibromyxoid tumor, is rare and in the past was believed to reflect diverse entities. We reviewed a series of 46 IMTs arising in the ureter, bladder, and prostate, derived primarily from a large consultation practice. There were 30 male and 16 females aged 3 to 89 years (mean 53.6). Lesions were 1.2 to 12 cm (mean 4.2). There was a history of recent prior instrumentation in 8 cases. Morphology was similar to that previously described for IMT occurring in this region, with the exception of 1 case that focally appeared sarcomatous. Polypoid cystitis coexisted in 5 patients (11%). Mitoses were typically scant (0 to 20/10 hpf, mean 1). Necrosis was seen in 14 (30%) cases. Invasion of the muscularis propria was documented in 19 (41%). By immunohistochemistry (IHC), lesions at least focally expressed anaplastic lymphoma kinase (ALK) (20/35, 57%), AE1/3 (25/34, 73%), CAM5.2 (10/15, 67%), CK18 (6/6, 100%), actin (23/25, 92%), desmin (15/19, 79%), calponin (6/7, 86%), caldesmon (4/7, 57%, rare cells), p53 (10/13, 77%), and most lacked S100 (0/14), CD34 (0/13), CD117 (2/13, 15%), CD21 (0/5), and CD23 (0/3). ALK gene alterations were detected by fluorescence in situ hybridization (FISH) in 13/18 (72%) tested cases, including 2 with prior instrumentation; 13/18 (72%) showed agreement between FISH ALK results and ALK protein results by IHC. Most bladder IMTs were managed locally, but partial cystectomy was performed as the initial management in 7 cases and cystectomy in 1 (1 IMT was initially misinterpreted as carcinoma, 1 IMT was found incidentally as a separate lesion in a cystectomy specimen performed for urothelial carcinoma). Follow-up was available in 32 cases (range 3 to 120 mo; mean 33; median 24). There were 10 patients with recurrences (2 with 2 recurrences). Recurrences were unassociated with muscle invasion or with ALK alterations. In 2 cases, tumors of the urinary tract (TURs) showing IMT preceded (1 and 2 mo, respectively) TURs showing sarcomatoid carcinoma with high-grade invasive urothelial carcinoma accompanied with separate fragments of IMT. Even on re-review the IMT in these 2 cases were morphologically indistinguishable from other cases of IMT, with FISH demonstrating ALK alterations in the IMT areas in one of them. Both these patients died of their carcinomas. Lastly, there was 1 tumor with many morphological features of IMT and an ALK rearrangement, yet overtly sarcomatous. This case arose postirradiation for prostate cancer 4 years before the development of the lesion, with tumor recurrence at 4 months and death from intra-abdominal metastatic disease at 9 months. In summary, urinary tract IMTs are rare and share many features with counterparts in other sites, displaying similar morphology and immunogenotypic features whether de novo or postinstrumentation. Typical IMTs can be locally aggressive, sometimes requiring radical surgical resection, but none of our typical cases metastasized, although they can rarely arise contemporaneously with sarcomatoid urothelial carcinomas. For these reasons, close follow-up is warranted.

Editorial Comment

It is controversial in the literature whether inflammatory myofibroblastic tumor of the urinary tract is an inflammatory or a neoplastic lesion. This is the reason for the vast list of synonyms: reactive pseudosarcomatous response, postoperative spindle cell nodule, inflammatory pseudotumor, nodular fasciitis, pseudomalignant spindle cell proliferation, pseudosarcomatous myofibroblastic proliferation, pseudosarcomatous myofibroblastic tumor, and inflammatory myofibroblatic tumor.

The lesion mimics both sarcomas and spindled carcinomas, the latter compounded by their expression of various cytokeratins (1). Considering that the lesion in the urinary tract has been benign in almost all series it would be similar to nodular fasciitis elsewhere. However, it differs by nodular fasciitis in its capacity to infiltrate deeply into the detrusor muscle (2).

The identification of ALK alterations in bladder lesions suggests that, despite the frequent similarity to nodular fasciitis, inflammatory myofibroblastic tumor is neoplastic (3). There is a clonal aberration typically involving chromosome 2p. This results in rearrangement of the ALK gene which codifies a receptor of tyrosine-kinase and hence over-expression of ALK-1 protein. This over-expression of the ALK protein is also seen in anaplastic large cell lymphomas.

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Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, Sao Paulo, Brazil

INVESTIGATIVE UROLOGY

Testicular Volume Measurement: Comparison of Ultrasonography, Orchidometry, and Water Displacement

Sakamoto H, Saito K, Oohta M, Inoue K, Ogawa Y, Yoshida H
Department of Urology, Showa University School of Medicine, Tokyo, Japan
Urology. 2007; 69: 152-7

Objectives: To determine the accuracy of orchidometry and ultrasonography for measuring the testicular volume by comparing the resultant measurements with the actual testicular volume in humans.
Methods: The testicular volume of 40 testes from 20 patients with prostate cancer (mean age +/- SD 74.5 +/- 7.5 years) was measured using the Prader orchidometer and ultrasonography before therapeutic bilateral orchiectomy. The ultrasound measurements of testicular volume were calculated using three formulas: length (L) x width (W) x height (H) x 0.52, L x W2 x 0.52, and L x W x H x 0.71. The actual testicular volumes were determined by water displacement of the surgical specimen.
Results: The mean actual testicular volume of the 40 testes was 9.3 cm3 (range 2.5 to 23.0). A strong correlation was found between the testicular volume calculated by the three ultrasound formulas and the actual volume ($r = 0.910$ to 0.965, $P < 0.0001$) and was stronger than the correlation with the Prader orchidometer ($r = 0.818$, $P < 0.0001$). The smallest mean difference from the actual testicular volume was observed with the formula L x W x H x 0.71, which overestimated the actual volume by 0.80 cm3 (7.42%). The measurements using the Prader orchidometer correlated with the actual testicular volume and with the testicular volume calculated using the three ultrasound formulas ($r = 0.801$ to 0.816, $P < 0.0001$). However, the orchidometer measurements had the largest mean difference from the actual testicular volume (6.68 cm3, 81.7%).
Conclusions: The results of this study have shown that measuring the testicular volume by ultrasonography is more accurate than by the Prader orchidometer, and the formula L x W x H x 0.71 was the most accurate for calculating the testicular volume.

Editorial Comment
This is a straightforward research work, which objectively demonstrates that ultrasonographic evaluation of testicular volume is accurate. The authors compared ultrasound evaluation by the ellipsoid volume formula (2

methods), a variation of the ellipsoid formula and orchidometry, with water displacement, that is the real volume (Laplace principle). Although the classical ellipsoid volume formula used in ultrasound equipment is accurate, the authors demonstrated that the best formula is a variant of the ellipsoid formula, called the Lambert empiric formula (V = Length × Width × Height × 0.71).

Dr. Francisco J.B. Sampaio
Full-Professor and Chair, Urogenital Research Unit
State University of Rio de Janeiro
Rio de Janeiro, RJ, Brazil

Immediate Improvement in Penile Hemodynamics after Cessation of Smoking: Previous Results

Sighinolfi MC, Mofferdin A, De Stefani S, Micali S, Cicero AF, Bianchi G
Department of Urology, University of Modena, Modena, Italy
Urology. 2007; 69: 163-5

Objectives: To assess the chronologic relationship between the cessation of smoking and the restoration of erectile function. Smoking is associated with an increased risk of erectile dysfunction.
Methods: Twenty active smokers (20 to 40 cigarettes/day) affected by erectile dysfunction (International Index of Erectile Function 5-item score less than 21) were enrolled in the study. The mean age was 40 years. All the patients underwent penile color Doppler ultrasonography during the basic and dynamic phases (10 microg prostaglandin E1). A second Doppler evaluation was performed 24 to 36 hours after cessation of smoking. The peak systolic velocity (PSV) and end-diastolic velocity (EDV) were recorded. The PSV and EDV cutoff value was 30 cm/s and 5 cm/s, respectively.
Results: Of the 20 patients, 10 (50%) had normal PSV values but only 5 (25%) had normal EDV values at the baseline Doppler evaluation. All the patients (100%) had normal PSV values at the second penile Doppler evaluation after smoking withdrawal, and 17 (85%) also had normal EDV values. The average PSV was 40.1 and 50.3 cm/s ($P = 0.09$) and the mean EDV was 6.8 and 2.4 cm/s ($P < 0.01$) at the baseline penile Doppler examination and after smoking withdrawal, respectively.
Conclusions: Within 24 to 36 hours of the cessation of cigarette smoking, the color Doppler parameters demonstrated a significant improvement in EDV and a trend toward an increase in PSV. Additional clinical evaluation is required to further characterize the expeditious improvement in erectile function after the cessation of smoking.

Editorial Comment

This is a very impressive study, on which the authors evaluated prospectively 20 current smokers (20 to 40 cigarettes/day) with a mean of 7 years of smoking history. It was found that after 24 to 36 hours of smoking cessation, all 20 patients (100%) had normal peak systolic velocity values and 17 (85%) had normal end-diastolic velocity values at Doppler examination. This study is pioneer on the evaluation of short-term effects of the cessation of cigarette smoking in penile hemodynamics parameters. It is impressive how rapidly smoking cessation can improve penile hemodynamics.

Dr. Francisco J.B. Sampaio
Full-Professor and Chair, Urogenital Research Unit
State University of Rio de Janeiro
Rio de Janeiro, RJ, Brazil

Effect of Extract of Phyllanthus Niruri on Crystal Deposition in Experimental Urolithiasis

Barros ME, Lima R, Mercuri LP, Matos JR, Schor N, Boim MA
Department of Medicine, Renal Division, Federal University of Sao Paulo, Sao Paulo, SP, Brazil
Urol Res. 2006; 34: 351-7

Phyllanthus niruri (Pn) is a plant that has been shown to interfere in the growth and aggregation of calcium oxalate (CaOx) crystals. In the present study we evaluated the effect of Pn on the preformed calculus induced by introduction of a CaOx seed into the bladder of male Wistar rats. Pn treatment (5 mg/rat/day) was initiated immediately or 30 days after CaOx seeding and thus in the presence of a preformed calculus. Animals were sacrificed 50 or 70 days after surgery. The resulting calculi were weighed and analyzed by X-ray diffraction, stereomicroscopy and scanning electronic microscopy. Precocious Pn treatment reduced the number (75%, $P < 0.05$) and the weight (65%, $P < 0.05$) of calculi that frequently exhibited a matrix-like material on its surface, compared to the untreated CaOx group. In contrast, Pn treatment in the presence of a preformed calculus did not prevent further calculus growth; rather, it caused an impressive modification in its appearance and texture. Calculi from Pn-treated animals had a smoother, homogeneous surface compared to the spicule shape of calculi found in the untreated CaOx group. XRD analysis revealed the precipitation of struvite crystals over the CaOx seed and Pn did not change the crystalline composition of the calculi. This suggests that Pn interfered with the arrangement of the precipitating crystals, probably by modifying the crystal-crystal and/or crystal-matrix interactions. Results suggest that Pn may have a therapeutic potential, since it was able to modify the shape and texture of calculi to a smoother and probably more fragile form, which could contribute to elimination and/or dissolution of calculi.

Editorial Comment

Phyllanthus niruri, is a plant used in Brazilian folk medicine. Its infusion tea is called “break-stone tea” and is widely used in Brazil for treatment of urolithiasis. The authors of this paper have been studying the effects of Phyllanthus niruri on urolithiasis at least for the last 10 years and have contributed a lot for the specialized literature (1-3).

In the present experimental study, the authors used a model of preformed calculus induced by introduction of a CaOx seed into the bladder of male Wistar rats. The authors elegantly demonstrated, by using X-ray diffraction, stereomicroscopy and scanning electronic microscopy, that precocious treatment with Phyllanthus niruri significantly reduced the number and the weight of calculi compared to the untreated CaOx seeding group. Also, on scanning electronic microscopy, in treated group, it was observed a homogeneous surface compared to the spicule shape of calculi found in the untreated CaOx group. These findings, together with previous findings from the same research group (1-3), suggest objectively that Phyllanthus niruri (“break-stone tea”) might have therapeutic potential for urolithiasis.

Interesting, in a recent published work from Italy, it was assessed the efficacy of Phyllanthus niruri after extracorporeal shock wave lithotripsy (ESWL) for renal stones (4). The authors evaluated prospectively 150 patients with renal stones that were as large as 25 mm and composed of calcium oxalate. All patients received 1 to 3 ESWL with Dornier Lithotriptor S. After treatment, 78 of 150 patients (52%) underwent therapy with Phyllanthus extract for at least 3 months (group 1). The other 72 of 150 patients (48%) were used as a control group (group 2). No significant difference in stone size between the 2 groups was found. Stone clearance was assessed after 30, 60, 90 and 180 days by abdominal X-ray and ultrasonography. Although no significant difference was found at the end point of the follow-up (180 days), for lower caliceal stones (56 patients) the stone-free rate was 93.7% in the treatment group and 70.8% in the control group ($p = 0.01$). The authors concluded that regular self-administration of Phyllanthus niruri after ESWL for renal stones results in an increased stone-free rate that appears statistically significant for lower caliceal location. Since ESWL for lower pole

stones is challenging and present poor results when compared to other locations stones (5), the efficacy and the lack of side effects make Phyllanthus niruri therapy suitable to improve overall outcomes after extracorporeal shock wave lithotripsy for lower pole stones.

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Dr. Francisco J.B. Sampaio
Full-Professor and Chair, Urogenital Research Unit
State University of Rio de Janeiro
Rio de Janeiro, RJ, Brazil

RECONSTRUCTIVE UROLOGY

Efficacy of the InVancetrade mark Male Sling in Men with Stress Urinary Incontinence

Fassi-Fehri H, Badet L, Cherass A, Murat FJ, Colombel M, Martin X, Gelet A
Department of Urology and Transplantation, Edouard Herriot Hospital, Lyon, France

Eur Urol. 2007; 51: 498-503

Objectives: To evaluate the efficacy and safety of the InVancetrade mark bulbourethral sling in male stress urinary incontinence.

Materials and Methods: Between June 2003 and April 2005, the InVancetrade mark bulbourethral sling was implanted into 50 patients with urinary incontinence after prostate surgery in 49 cases and pelvic trauma in 1 case. The patients were monitored and evaluated in a prospective manner (continence, tolerance, and satisfaction). The treatment was considered to be successful if the patient stopped wearing any kind of continence pad (patient cured) or only one pad per day (patient improved), with no de novo urinary disorders and without significant postvoid residual urine. Patient satisfaction with the procedure was assessed.

Results: After a median follow-up of 6 mo, 50% of patients were dry, 26% had improved, and 24% suffered treatment failure. The success rates for the patients with severe incontinence and those who had undergone radiation therapy were 50% and 25%, respectively. All patients who were dry or had improved were satisfied and presented no obstructive or irritative de novo urinary disorders. The overall success rate for the 51 procedures conducted was 74.5%. Six cases of transitory acute urine retention and six cases of persistent perineal pain were reported. Explantation was necessary because of suppuration of the sling in three patients and of a de novo irritative urinary disorder in one patient. No cases of pubic osteitis or urethral erosion were reported.

Conclusions: The InVancetrade mark bulbourethral sling procedure makes it possible to treat stress urinary incontinence after prostate surgery with satisfactory and lasting short-term results. Severe incontinence and a past history of pelvic radiation therapy seem to be factors contributing to the failure of this procedure.

Editorial Comment

Male urinary stress incontinence is often an aftereffect of a necessary prostate treatment. Such as transurethral resection of the benign enlarged prostate, radical prostatectomy or irradiation treatment for prostate cancer.

If iatrogenic caused incontinence does not disappear within a year under conservative treatment (pelvic floor exercise and the use of drugs like duloxetin) surgical approaches need to be discussed with the patient. Most of these patients are afraid of the implantation of an artificial sphincter hoping for a minimal invasive approach to treat their urinary stress incontinence.

Besides injectables (1), which demonstrate usually only a short term improvement, micro balloons and different kinds of urethral sling were introduced as a treatment option.

Fessi-Fehri et al. (2) extended their study of the use of a bow-anchored sling. Although the outcome seems to be almost identical in comparison to their first report with a follow-up of 3 months the enlarged groups of now 50 patients have a similar pleasing outcome of success even with a 6 months mean follow-up (1 - 22 months). It is remarkable that those who have now a follow–up of over 6 months 16 of 17 patients (94%) were dry or at least improved.

The authors mention a critical point: that those patients after radiotherapy or with the severe incontinence might still benefit most with an artificial sphincter. With the increased anatomical knowledge of the external urethral sphincter (3) and the satisfying published outcome of the TOT in female, the Advanced Male Sling System® of AMS might be the needed male version. It was just introduced to clinic but its primary data still needs to be confirmed. The attending urologist can offer today a cascade of treatment options, which might even further improve the outcome in a combination based on the cause of the urinary incontinence and its severity.

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Dr. Karl-Dietrich Sievert &
Dr. Arnulf Stenzl
Department of Urology
Eberhard-Karls-University Tuebingen
Tuebingen, Germany

The Hormonal Regulation of Cutaneous Wound Healing

Gilliver SC, Ashworth JJ, Ashcroft GS
Faculty of Life Sciences, Michael Smith Building, M13 9PT Manchester, United Kingdom
Clin Dermatol. 2007; 25: 56-62

Conditions of impaired wound healing in the elderly are associated with substantial morbidity and mortality and impose a significant financial burden upon the world's health services. The findings of a series of recent studies have served to highlight the contrasting contributions made by sex steroid hormones to the regulation of cutaneous repair processes. Although estrogens accelerate healing, the actions of the "male" sex hormones 5alpha-dihydrotestosterone and testosterone are primarily deleterious. The shift that occurs in the balance between serum estrogen and androgen levels as a normal feature of human aging may therefore have important consequences for fundamental tissue repair processes.

Editorial Comment

The paper outlines nicely the effect of sex hormones on wound healing. Topical and systemic estrogen applications have been shown to both increase acute healing and to prevent the development of a chronic wound status. A similar beneficial effect for wound healing was seen with the precursor of both androgenic and estrogenic effector molecules, dehydroepiandrosterone (DHEA). Both estrogens and DHEA dampen local inflammation and promote matrix deposition. The modulation of inflammatory responses by sex hormones is partially regulated by modulating macrophage function, which in turn leads to changes in TNF-alpha production, macrophage migration inhibitory factor secretion, and IL-6 expression.

In contrast, androgens seem to be negative regulators for wound healing suggesting that they retard repair processes and enhance the local inflammatory response. All surgeons including those dealing with flaps used in reconstructive urology are confronted with impaired wound healing possibly resulting in chronic wound healing states. Topical and systemic estrogen treatment as well as dehydroepiandrosterone may help to overcome some of the problems of flap or other reconstructive interventions and its sometimes peculiar problems regarding healing. This may be of particular importance in elderly patients were particularly estrogen and DHEA deficiency is thought to be the cause of age-related impaired wound healing. One should also think about using systemic hormonal replacement therapy in female patients prior to complex reconstructive surgery in order to reduce chronic wound problems.

Dr. Karl-Dietrich Sievert &
Dr. Arnulf Stenzl
Department of Urology
Eberhard-Karls-University Tuebingen
Tuebingen, Germany

UROLOGICAL ONCOLOGY

Outcome of Surgery for Clinical Unilateral T3a Prostate Cancer: A Single-Institution Experience

Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H
Department of Urology, University Hospitals KULeuven, Leuven, Belgium
Eur Urol. 2007; 51: 121-8; discussion 128-9

Objectives: The optimal management of locally advanced prostate cancer (cT3) is still a matter of debate. The objective of this study is to present 10-year outcomes of radical prostatectomy (RP) in unilateral cT3a disease. Patients and Methods: Between 1987 and 2004, 2273 patients underwent RP at our institution. Two hundred and thirty-five (10.3%) patients were assessed as unilateral cT3a disease by digital rectal examination. Thirty-five patients who received neoadjuvant treatment before surgery were excluded from further analysis. Mean

follow-up was 70.6 months. Kaplan-Meier survival analysis was used to calculate the biochemical progression-free survival (BPFS), clinical progression-free survival (CPFS), cancer-specific survival (CSS), and overall survival (OS) rates. Cox uni- and multivariate regression analyses were used to identify predictive factors in BPFS and CPFS.
Results: Clinical overstaging (pT2) occurred in 23.5%. One hundred and twelve (56%) patients received adjuvant or salvage therapy. OS at 5 and 10 years was 95.9% and 77.0%, respectively, and CSS was 98.7% and 91.6%. BPFS at 5 and 10 years was 59.5% and 51.1%, respectively, and CPFS was 95.9% and 85.4%. Margin status was a significant independent predictor in BPFS; cancer volume was a significant independent predictor in CPFS.
Conclusions: Clinically advanced prostate cancer is still frequently overstaged. In a well-selected patient group with locally advanced prostate cancer, RP—with adjuvant or salvage treatment when needed—can yield very high long-term cancer control and survival rates. Margin status and cancer volume are significant predictors of outcome after RP.

Editorial Comment
The outcomes of clinically unilateral T3 cancer after surgical treatment are presented. In 22% the patients received adjuvant and in 34% they received salvage hormonal or radiation treatment.

Generally the outcomes are relatively good with only 10% cancer mortality after 10 years. The authors claim a high rate of overstaging in 23.5 % which leaves some doubt in the preoperative staging procedures, e.g. was TRUS performed preoperatively? Further aspects still might be debatable and are also addressed in the comments to this paper. At least one point of debate might be added. What happened to bilateral T3 patients and why were these excluded? The authors compare their results with radiotherapy results from historical trials but I do not remember this exclusion criterion in these radiotherapy trials.

In conclusion, both surgical and radiation therapy approaches seem justified in the treatment of locally advanced prostate cancer.

Dr. Andreas Bohle
Professor of Urology
HELIOS Agnes Karll Hospital
Bad Schwartau, Germany

Discrepancy between Clinical and Pathologic Stage: Impact on Prognosis after Radical Cystectomy

Shariat SF, Palapattu GS, Karakiewicz PI, Rogers CG, Vazina A, Bastian PJ, Schoenberg MP, Lerner SP, Sagalowsky AI, Lotan Y
Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9110, USA
Eur Urol. 2007; 51: 137-49; discussion 149-51

Objectives: We compared clinical and pathologic staging in a large, contemporary, consecutive series of patients who were treated with radical cystectomy and pelvic lymphadenectomy, and determined the effect of stage discrepancy on outcomes.
Methods: We collected retrospective data from 778 consecutive patients with bladder transitional cell carcinoma who were treated with radical cystectomy and pelvic lymphadenectomy, and for whom the clinical and pathologic stage were available.

Results: Pathologic upstaging occurred in 42% of patients, and pathologic downstaging occurred in 22%. Forty percent of patients with non-muscle-invasive clinical stage had muscle-invasive pathologic stage. Thirty-six percent of patients with organ-confined clinical stage had non-organ-confined pathologic stage (> or = pT3N0 or pTanyN-positive). Patients with higher clinical stage were more likely to be upstaged to non-organ-confined disease ($p < 0.001$). Patients were stratified into three groups: pathologically upstaged, same clinical and pathologic stage, and pathologically downstaged. When adjusted for the effects of standard postoperative features, upstaged patients were at a significantly higher risk of disease recurrence and bladder cancer-specific death than patients who had the same pathologic and clinical stage, who in turn were at significantly higher risk than downstaged patients. This observation remained true within each clinical stage strata. Within each pathologic stage strata, clinical stage did not substratify into different risk groups.
Conclusions: Clinical to pathologic stage discrepancy is a relatively common finding after extirpative surgery for bladder cancer. Clinical outcomes after radical cystectomy are largely driven by pathologic stage. Better clinical staging is necessary to improve patient evaluation and management.

Editorial Comment
A large series of 778 patients with infiltrative bladder cancer undergoing radical cystectomy was retrospectively analysed and the impact of staging error calculated.

Most interestingly – and not debated much in this paper – is the fact that the percentage of correct peroperative staging declined (!) over the years with correct staging around 44% until 1994 and around 35% and lower from 1995 to 2003. What happened in these periods? Was there an institutional change or did surgeons not perform TURB as thoroughly as before?

Notably, downstaging moderately decreased from 26% to around 20% during these years whereas upstaging sharply increased (!) from around 28% to 43% and 49% in the later periods mentioned above.

The outcomes of pathologically staged cancer finally were in the expected range with rather good results showing roughly 80% bladder cancer specific survival in organ confined disease as compared to 37% in non organ-confined disease.

These data again seem to justify adjuvant chemotherapy in this high-risk group of patients.

Dr. Andreas Bohle
Professor of Urology
HELIOS Agnes Karll Hospital
Bad Schwartau, Germany

NEUROUROLOGY & FEMALE UROLOGY

Voiding Dysfunction Following Removal of Eroded Synthetic Mid Urethral Slings

Starkman JS, Wolter C, Gomelsky A, Scarpero HM, Dmochowski RR
Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA
J Urol. 2006; 176: 1040-4

Purpose: Voiding dysfunction following genitourinary erosion of synthetic mid urethral slings is not clearly reported. We investigated the incidence of voiding dysfunction in patients following sling excision due to vaginal, urethral or intravesical mesh erosion.

Materials and Methods: Retrospective review identified 19 patients with genitourinary erosion of polypropylene mesh slings. Comprehensive urological evaluation was performed in all patients, and perioperative and postoperative data were analyzed. Voiding dysfunction was defined as refractory storage symptoms, emptying symptoms and pelvic pain. All subsequent medical and surgical interventions were recorded.
Results: In 19 patients a total of 11 vaginal, 7 intravesical and 5 urethral erosions occurred. Mean patient age was 52 years (range 32 to 69) and average followup was 8.4 months (range 3 to 34). Average time from symptom onset to sling removal was 10.1 months (range 1.5 to 38). Of the 19 patients 14 (74%) presented with multiple symptoms. Symptoms varied, including refractory pain, recurrent infections and bladder storage/emptying dysfunction. Urodynamic studies were abnormal preoperatively and postoperatively in 9 of 13 (69%) and 4 of 6 patients (67%), respectively. Following surgery lower urinary tract symptoms resolved completely in only 4 of the 19 patients (21%). Stress incontinence recurred in 8 of the 19 patients (42%). Five patients underwent simultaneous pubovaginal sling, of whom none had recurrent stress urinary incontinence. Only 9 patients (47%) considered themselves dry with no pads following surgery. Four patients required further surgery for refractory voiding symptoms.
Conclusions: Voiding dysfunction is not an uncommon finding after sling excision in the setting of genitourinary erosion. It may cause additional patient morbidity.

Editorial Comment

The authors give a sobering report on their experience with voiding dysfunction after erosion of synthetic mid-urethral slings. Their study included vaginal, vesical, and urethral erosions. The patient population was relatively young (average age 52) with average follow-up after intervention being less than 1 year. This report of persistent voiding dysfunction following removal of the eroded material as well as the high rate of incontinence after reparative surgery can be deflating to a treating physician. The incidence of recurrent incontinence is somewhat higher than that reported for transobturator suburethral tape erosion and subsequent explantation (1). The authors point out that in their experience, preoperative urodynamics prior to the removal of the erosion may be of marked value. In addition, it is noted that the presentations of tape erosion may be quite variable necessitating a high index of suspicion and a careful evaluation for appropriate diagnosis. One may heed the authors' advice that aggressive mesh removal for vaginal extrusion is not needed in all situations and that surgical judgment should be exercised. They also do debate the need for synchronous placement of pubovaginal sling at the time of mesh removal to prevent recurrent stress urinary incontinence.

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Dr. Steven P. Petrou
Associate Professor of Urology
Chief of Surgery, St. Luke's Hospital
Associate Dean, Mayo School of Graduate Medical Education
Jacksonville, Florida, USA

Objective and Subjective Cure Rates after Trans-obturator Tape (OBTAPE) Treatment of Female Urinary Incontinence

Deval B, Ferchaux J, Berry R, Gambino S, Ciofu C, Rafii A, Haab F
Service de Gynecologie, Hopital Beaujon, Assistance Publique - Hopitaux de Paris (AP-HP), Universite Paris VII, Clichy, France
Eur Urol. 2006; 49: 373-7

Objective: To evaluate the safety and efficacy of a thermally bonded nonwoven polypropylene mesh in a transobturator suburethral tape procedure (OBTAPE), Mentor-Porges, Le Plessis Robinson, France) for women with stress urinary incontinence.
Methods: Between January 2003 and January 2005, 129 consecutive women (mean age 57.2 years) underwent OBTAPE in two academic centers. All the patients had stress urinary incontinence preoperatively. Detrusor instability was ruled out by cystometry. The women were evaluated 1, 6 and 12 months postoperatively. The objective cure rate was evaluated by clinical examination and the subjective cure rate was assessed using the KHQ and BFLUTS questionnaire.
Results: Mean follow-up was 17.2 +/- 4.7 months (range 4 to 28 months). The objective and subjective cure rates were respectively 89.9% and 77.5%. Most of the patients received general anesthesia (85.3%). Urinary retention was observed in two women (1.5%), necessitating tape adjustment. Voiding difficulties were observed in 7 cases (5.4%) necessitating intermittent self-catheterization for 4.2 +/- 2.4 days (range 1 to 7 days). Seven patients developed vaginal erosion (one with vaginal extrusion, and two with an obturator abscess). Complete mesh removal was necessary in 6 patients, four of whom had recurrent stress urinary incontinence.
Conclusions: Our results suggest that the OBTAPE is an effective treatment for women with stress urinary incontinence. However, vaginal mesh erosion occurred in 6.2% of women, and this implies the need for careful follow-up.

Editorial Comment

The authors reviewed the effectiveness of the transobturator procedure using the OBtape® material. The authors found overall cure rates that were very competitive with other suburethral sling procedures but noted a relatively high erosion rate.

This publication evaluated a fairly young patient population (average age 57.1) and followed the patients for a minimum of six months. Objective cure of stress incontinence was judged on fairly strict criteria: both clinical and urodynamic examinations were utilized though it is unclear when the urodynamic examinations were performed postoperatively. In addition to the objection evaluation, the patients were asked to judge their surgical result on a subjective basis. Performance of the operation was very efficient with a mean operating time being a little less than 10 minutes. Objective cure rates were approximately 90% with subjective cure rates being somewhat less at 78%. Of interest is that two-thirds of the patients had resolution of their preoperative urge symptoms while one-third has persistence of same. This mirrors closely that reported for other surgical procedures (1). That this operation usually necessitates less vaginal dissection opposes the argument that the urge component may be lessened by incidental neural ablation occurring during the vaginal dissection (2). This high erosion rate using the OBtape® has been reported by other surgeons leading to the discontinuation of use of this material; in response, there has been a progression to new tapes such as Aris™ that is knitted and has a larger pore size of 550 x 170 microns. Other authors have stated that erosion may be material based and not really a technical problem (3). This paper does reinforce the ease and efficacy of this procedure.

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Dr. Steven P. Petrou
Associate Professor of Urology
Chief of Surgery, St. Luke's Hospital
Associate Dean, Mayo School of Graduate Medical Education
Jacksonville, Florida, USA

PEDIATRIC UROLOGY

Natural History of Patients With Multicystic Dysplastic Kidney-What Followup Is Needed?

Onal B, Kogan BA
Division of Urology, Albany Medical College, Albany, New York, USA
J Urol. 2006; 176: 1607-11

Purpose: Most clinicians recommend followup with annual ultrasound for patients with multicystic dysplastic kidney. The aim of this study was to determine whether followup ultrasound provides any clinical benefit.
Materials and Methods: We retrospectively reviewed the charts of 73 patients who were diagnosed with multicystic dysplastic kidney between October 1991 and August 2005. Data were analyzed with respect to patient characteristics and followup information.
Results: We identified 61 patients (43 boys and 18 girls) with adequate followup. A total of 49 patients (80%) were diagnosed prenatally and 12 (20%) postnatally. Associated urological anomalies were noted in 16 patients (26%). Median followup was 2.6 years (range 6 months to 37.5 years). Ultrasound examinations showed complete involution in 25 patients (41%) and partial regression in 18 (30%). The size of the multicystic dysplastic kidney increased in 1 patient (1.6%) and was unchanged in 17 (28%) without any pathological manifestations. Median age at complete involution was 2.1 years (range 36 days to 13.7 years). Patients with contralateral compensatory hypertrophy had more rapid complete involution. Urinary tract infection developed in 6 patients, of whom 1 was ultimately found to have reflux and 1 had ureteropelvic junction obstruction.
Conclusions: In our patients with unilateral multicystic dysplastic kidney ultrasound provided little clinically important information. Our data and a review of the literature suggest that once the diagnosis is made, no urological followup is needed. The primary care provider should monitor patients with multicystic dysplastic kidney for hypertension, abdominal mass and urinary tract infection.

Editorial Comment
This is an interesting review of 73 patients between 1991 and 2005 diagnosed with multicystic kidney disease. Of these 61 patients, 43 boys and 18 girls, had follow up with ultrasound postnatally and VCUG or renal scan.

Median age at diagnosis was 1.5 years and median follow up was 2.6 years with the median number of ultrasounds per patient was 4. Associated urologic anomalies were found in 16 patients. Most were vesicoureteral reflux. Four had ureteroceles and 1 had a contralateral ureteropelvic junction obstruction. The authors evaluated their patients thoroughly for hypertension and development of kidney tumors and none of their patients developed either. Only one of their patients had an increase in size in the multicystic kidney. They conclude that multicystic dysplastic kidney patients should have a postnatal ultrasound and VCUG and only patients with associated urologic anomalies should have continual follow up.

This data seems to mirror that which is seen in the medical literature and there is very little evidence that multicystic dysplastic kidney patients will develop hypertension at any increased rate or develop a kidney tumor. Many have recommended that the ultrasounds be done at least until age 8 or even puberty. In this study, the actual follow up is relatively short but their lack of findings seems to validate their conclusions that routine imaging is unnecessary.

Dr. Brent W. Snow
University of Utah Health Sci Ctr
Division of Urology
Salt Lake City, Utah, USA

Impact of Patient Age on Distal Hypospadias Repair: A Surgical Perspective

Perlmutter AE, Morabito R, Tarry WF
Division of Urology, West Virginia University School of Medicine, Morgantown, West Virginia, USA
Urology. 2006; 68: 648-51

Objectives: To assess whether the age at which the initial hypospadias repair is performed influences the complication rate of hypospadias repair.
Methods: The records of 325 consecutive patients who underwent initial hypospadias repair were reviewed. The patients with glanular and coronal hypospadias underwent repair with either meatoplasty and glanuloplasty or a glans approximation procedure. Patients with subcoronal hypospadias and penile hypospadias underwent repair with tubularized incised plate urethroplasty. The patients were divided into 6-month age groups, and the complication rates were analyzed by age group using the chi-square test.
Results: A total of 325 hypospadias repairs were performed from January 1999 to January 2005 by a single surgeon. Of the 325 cases, 194 tubularized incised plate procedures were performed, 69 meatoplasty and glanuloplasty procedures were performed, and 53 glans approximation procedures were performed. Nine tubularized island flap urethroplasties performed for penoscrotal hypospadias were excluded because we did not perform a significant number of proximal urethroplasties. Nineteen patients (6.0%) developed urethrocutaneous fistulas and six (1.9%) demonstrated dehiscence. Overall, 2 patients (2.2%) who underwent surgical repair within the first 6 months of age developed complications compared with 23 patients (10.3%) who underwent initial hypospadias repair when they were older than 6 months of age ($P = 0.006$).
Conclusions: Tubularized incised plate, meatoplasty and glanuloplasty, and glans approximation urethroplasty are all excellent options for the surgical correction of hypospadias in the appropriately selected patient. The results of our study have indicated that complications are minimized when hypospadias repair is performed when the patient is 4 to 6 months of age.

Editorial Comment

This article reviews 316 cases of distal hypospadias repair from 1999-2005. Patients underwent a tubularized incised plate urethroplasty, meatal advancement glanuloplasty or a glans approximation procedure, and were stratified into categories. The first category was 4-6 months of age and then after that, six month intervals, and their complications were compared.

Only two complications occurred in the 92 patients done between 4-6 months of age. 15 complications occurred between 7 and 12 months and two between 13 and 18 months. There was a statistical difference between complications in the 4-6 month group and any group thereafter. This was especially obvious in the tubularized incised plate urethroplasty group.

Currently for many reasons, the American Academy of Pediatrics has recommended genital surgery be performed between 6 and 12 months of age. This article brings into question whether this recommendation should be pushed a few months earlier for the benefits of the repair. As pediatric anesthesia has made great progress in the last couple of decades, the risk to infants is much less and similar during each of these age groups. This a piece of information that is interesting to consider, however it is difficult to understand on a physiologic basis, how a few months of age would make a difference in the healing process and complications of the patients.

Dr. Brent W. Snow
University of Utah Health Sci Ctr
Division of Urology
Salt Lake City, Utah, USA